# MRC/DH/MHRA Joint Project

# Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

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## Executive Summary


This paper is the outcome of a risk-stratification project initiated by an ad-hoc working group under the auspices of DH, MHRA and MRC to address key issues for clinical trials in the UK. The proposals outlined in this paper were developed with input from a wide range of key stakeholders, including:

- academic researchers
- clinical trial managers
- research governance managers
- MHRA assessors
- Good Clinical Practice (GCP) Inspectors.

Membership of the Ad-Hoc Working Group and the Risk-Stratification Sub-Group are provided in Appendix 3.

The proposals focus on the core set of risks inherent in a trial protocol, which impact on participant safety and rights, and the reliability of the results.

The current regulatory framework in the UK/EU allows for a range of risk-adapted approaches that may simplify the processes for initiating and conducting some clinical trials. These adaptations are largely related to how much is known about the investigational medicinal product (IMP). A simple risk categorisation is proposed, based on the marketing status of the IMP and standard medical care. Using a simple categorisation of three risk types it is possible to highlight, particularly for lower risk trials, where simplification is possible, resulting in a more risk proportionate approach. These are described in Appendix 1 and include:

- the need for authorisation by the competent authority
- the content of the Clinical Trials Authorisation (CTA) application
- IMP management
- safety surveillance
- trial documentation.
- GCP Inspection

The risk associated with the IMP should also determine the trial procedures for monitoring the safety of participants. It is proposed that the IMP risk category and safety monitoring plan be submitted to the MHRA with the Clinical Trial Authorisation to ensure that there is shared understanding on this key aspect of the trial

The other aspects of clinical trial design and methodology considered in this paper include:

- safety risks from clinical procedures specified by the protocol
- risks related to participant rights
- risks to the reliability of trial results.

The IMP risk category has implications for level of risk associated with these, but does not determine them. A risk assessment process is proposed to identify potential vulnerabilities in trial design and methodology, and to prepare a trial management and monitoring plan to minimise the risks; this is outlined in Appendix 2.

Once developed, the risk assessment and associated management/monitoring plans would form the basis of a common understanding by all stakeholders on the risks for that trial, and facilitate a risk-proportionate approach to the trial activities.

## Background to the Project

Following the implementation of the Clinical Trials Directive 2001/20/EC (CTD) in 2004, compliance with the principles of GCP became a legal requirement for everyone in the European Union involved in the conduct of a clinical trial with a medicinal product and was translated into national law in each Member State (MS). This was further developed by the publication and implementation of the GCP Directive 2005/28/EC in 2005. The CTD applies to all clinical trials of medicinal products in Europe, from "first in man" trials to pragmatic comparisons of commonly used treatments. Whilst the CTD recognised that there were commercial and non-commercial sponsors, it made no distinction between them with regard to the GCP requirements. The European Commission proposed to publish 'specific modalities' guidance for non-commercial trials to indicate where certain aspects of GCP could be 'relaxed' for these trials specifically. This guidance, although consulted on, has never been published. This has contributed to non-commercial trialists, and those who sponsor their research in particular, believing that they must manage all aspects of trial conduct and GCP in a similar way to commercial sponsors (Pharmaceutical industry)..

Despite there being a degree of flexibility in how the principles of GCP should be applied and a range of risk-adapted approaches to trial conduct within the CTD, many organisations have had concerns about not meeting all of the statutory requirements for the conduct of clinical trials. This has resulted in some organisations, particularly those within the public sector, becoming reluctant to participate in clinical trials and in others taking a risk-averse approach and requiring additional processes which have increased the cost and complexity of clinical trials unduly.

This project was established to help facilitate a risk-proportionate approach in the UK in applying the principles of GCP to the various types of clinical trial, within the context of the current regulatory framework in the EU by:

1. Developing a process to facilitate the agreement of key stakeholders on the level of risk associated with a clinical trial.
2. Identifying how risk-adapted approaches for clinical trials can be achieved within the current regulatory framework
3. Developing a risk assessment tool, with guidance principles on how to manage and conduct clinical trials of investigational medicinal products (IMPs) in a risk-proportionate way.

## Risk in Clinical Trials

This can be defined as the likelihood of a potential hazard occurring and resulting in harm to the participant and/or an organisation, or to the reliability of the results. A clinical trial commonly involves several different organisations, and each must consider its specific

responsibilities/duties with respect to the trial and the level of risk in relation to these. For example:

- a funder considers the scientific and financial risks
- a sponsor is concerned about the legal and reputational risks
- a healthcare organisation considers the compatibility of the trial with its duty of care to patients.

For every trial, however, there is also a core set of risks inherent to the protocol that relate to the safety of the participants and the integrity/reliability of the results. All organisations involved need to understand these risks so that the control measures, resources, procedures and processes implemented during the trial ensure the safety of the trial participants, and lead to high-quality results.

Other factors contributing to the overall risks associated with an individual clinical trial, such as those related to its funding, the qualifications of the trial team conducting it, or the suitability of the host sites, are acknowledged but will not be considered in this paper. They will, however, contribute to the individual study risk assessments performed by sponsors, investigators, funders and site managers, and other guidance may be available to support this. For instance, the National Institute of Health Research (NIHR) Research Support Services framework provides a set of tools and Standard Operating Procedures (SOPs) to assist sponsoring and hosting sites to assess these aspects of risk.

There have been attempts in the past to categorise and score a number of the individual risks associated with a trial, and integrate these scores into a single risk score for the trial ( **Refs**). Although this approach potentially provides a way of describing a trial in relation to total risk, it has proved difficult to use in practise and hasn't provided practical guidance in relation to risk adaptations that may be possible.

## Risk Assessment

This is essentially a process of identifying the potential hazards associated with that trial, and assessing the likelihood of those hazards occurring and resulting in harm. This risk assessment will include:

- the risks to participant safety in relation to the IMP
- all other risks related to the design and methods of the trial (including risks to participant safety and rights, as well as reliability of results)

### 1. Risks to participant safety in relation to the IMP

Within a particular clinical trial, these can be categorised in relation to how much is known about the medicine(s) being investigated. These potential risks should be assessed relative to the standard of care for the relevant clinical condition and the level of clinical experience with the intervention rather than the patients' underlying illness or the recognised adverse effects of the intervention.

The potential risks should be balanced against the level of risk that a trial participant would be exposed to outside of the trial. We propose a three-level categorisation, based on the classification put forward by Brosteaunu and colleagues in the ADAMON Project, (ref).

- Type A = No higher than the risk of standard medical care
- Type B = Somewhat higher than the risk of standard medical care
- Type C = Markedly higher than the risk of standard medical care

A pragmatic approach to achieving this would be to use the marketing authorisation status of the medicines being investigated, as proposed in Table 1.

This simple method for categorising the risk associated with the IMP allows for several risk adaptations within the scope of the CTD. For lower-risk trials, this simplifies the requirements

for both obtaining regulatory approvals and conducting the trial. This is further expanded in Appendix 1. In addition, the implications of the IMP risk category for the monitoring of participant safety and the clinical trial are outlined in Appendix 2.

| **Trial Categories based upon the potential risk associated with the IMP** | **Examples of types of clinical trials** |
|---|---|
| ***Type A**: no higher than* that of standard medical care | Trials involving medicinal products licensed in any EU Member State if:<br>▪ they relate to the licensed range of indications, dosage and form<br>or, they involve off-label use (such as in paediatrics and in oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines |
| ***Type B**: somewhat higher* than that of standard medical care | Trials involving medicinal products licensed in any EU Member State if:<br>▪ such products are used for a new indication (different patient population/disease group) or<br>▪ substantial dosage modifications are made for the licensed indication or<br>▪ if they are used in combinations for which interactions are suspected<br>Trials involving medicinal products not licensed in any EU Member State if<br>▪ the active substance is part of a medicinal product licensed in the EU<br>(A grading of TYPE A may be justified if there is extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population)* |
| ***Type C**: markedly higher* than that of standard medical care | Trials involving a medicinal product not licensed in any EU Member State<br>(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)* |

**Table 1** (adapted from Adamon paper, excluding non-pharmacological interventions[1])

**If a grading other than those indicated is felt to be justified the rationale and evidence should be presented in the CTA application*

## 2. All other risks related to trial design and methods

The IMP risk category has implications for all the other risks, but does not determine them. IN other words, a Type A trial from an IMP perspective does not mean all other risks are low. The risks associated with participant rights and reliability of results are multi-factorial, and less amenable to simple categorisation at the trial level. The se risks must be assessed independently of the risks related to the IMP; in fact, an understanding of these will help direct what mitigation activity is required in the conduct of the trial and collection of the data. This approach is described in more detail in Appendix 2.

The design of a study has a major impact on the quality of the results; the more robust the design the less dependence there is on quality control and assurance measures for reliable results. Of critical importance is the identification of areas of potential vulnerability in trial design and planned methodology, which may require mitigation activities to ensure the reliability of the trial results and to protect participants' rights.

The proposed risk assessment process should be initiated by the chief investigator/protocol author at an early stage in protocol development. It should also be reviewed by other key stakeholders, such as the sponsor, funders and other investigators, to agree on the main risks inherent in the trial protocol. A plan to mitigate or manage these risks should be developed, either as part of the trial protocol or outlined in associated documents (such as a monitoring plan). Once developed, it is envisaged that the risk assessment and associated mitigation/monitoring plans will form the basis of a common understanding and dialogue by all stakeholders on the risks for that trial, and allow for a risk-proportionate approach to all trial activities.

Active sponsor and trial team oversight during the course of the trial will be essential in any risk-adapted model. This will ensure that escalation/moderation of activity in response to incoming data and feedback on trial progress/conduct can occur, as appropriate.

[1] Brosteanu et al. Risk analysis and risk adapted on-site monitoring in non-commercial clinical trials. *Clinical Trials* 2009: 585-596

## Appendix 1

## Guidance on risk-adapted approaches within the scope of the Clinical Trials Directive

The regulatory framework in the EU/UK provides for a range of risk-adapted approaches that simplify the processes involved in initiating and managing a clinical trial. This is particularly useful when investigating licensed medicines as these are principally related to the IMP risk category. Using the risk-categorisation method described in Table 1 above, Table 2 highlights the spectrum of potential risk associated with IMPs and the range of regulatory requirements that may be adapted.

Increasing potential risk of IMP

| Are Risk Adaptions possible? | Non-Interventional | Type A | Type B | Type C |
|---|---|---|---|---|
| **1. Reduced MHRA role for approval** | * | Yes | No | No |
| **2. Content of application** | * | Yes | (Yes) | No |
| **3. Labelling** | * | Yes | (Yes) | (Yes) |
| **4. Safety Surveillance** | * | Yes | (Yes) | No |
| **5. IMP management** | * | Yes | (Yes) | (Yes) |
| **6. Documentation** | * | Yes | (Yes) | No |
| **7. GCP Inspections** | * | Yes | (Yes) | (Yes) |

**Table 2**

***Key***: *Yes – possible; (Yes) – may be possible on case by case basis;*
*No – little, if any flexibility in requirements; * no specific clinical trial regulatory requirements*

## Non-Interventional trials

Some trials of medicines that appear to fall within the scope of the CTD will meet the criteria for a non-interventional trial, as defined in the Directive. These criteria are:

a) products that are prescribed in the usual manner, in accordance with the terms of authorisation;
b) assignment of any patient involved in the study to a particular therapeutic strategy is not decided in advance by a protocol, but falls within current practice;
c) the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study;
d) no diagnostic or monitoring procedures are applied to the patient s included in the study, other than those ordinarily applied in the course of the particular therapeutic strategy in question; and
e) epidemiological methods are to be used for the analysis of the data arising from the study.

If all of these criteria are met for a particular trial then the trial falls outside of the scope of the CTD and there are no formal regulatory requirements to be met. More information on how to apply these criteria can be found on the MHRA website.

Typically, sponsors conducting non-interventional trials in the NHS would need to obtain the approval of a Research Ethics Committee before commencing. Also, although the CTD does not apply and there are no regulatory requirements to meet, most institutions where this work

will be conducted may have local requirements/SOPs that address the standards to be met in many of the areas.

## Interventional Trials

All interventional trials fall within the scope of the CTD, however, Table 3 identifies the specific areas where it may be possible to apply risk adaptations.

| Risk Adaptions | Areas impacted |
|---|---|
| **1. Reduced MHRA role in approvals** | **Notification v Approval** |
| **2. Content of application** | **a) IMP dossier**<br>**b) Investigator's Brochure**<br>**c) Good Manufacturing Practice (GMP) Compliance** |
| **3. Labelling of trial drugs** | **a) Need for trial labelling**<br>**b) Content of labelling** |
| **4. Safety Surveillance** | **a) Adverse Drug Event recording/reporting**<br>**b) Safety Monitoring** |
| **5. IMP management** | **a) Tracking and Accountability**<br>**b) Storage** |
| **6. Documentation** | **a) Trial Master File (TMF) Content**<br>**b) Essential Documents retention times** |
| **7. GCP Inspections** | **a) Organisation and selection processes for routine GCP systems inspection**<br>**b) Inclusion in routine GCP inspection reviews at the study level**<br>**c) Frequency and duration of inspections** |

**Table 3**

### 1. Reduced MHRA role for approvals

All interventional trials of an IMP conducted in the UK require an approved Clinical Trial Authorisation (CTA) from the MHRA before they may commence.

From 1st April 2011 the majority of Type A trials conducted in the UK will only require to be notified to the MHRA. This will involve the sending of the standard EudraCT application form and accompanying documents in the usual way by the applicant. This will be acknowledged by the MHRA with an accompanying note to say that the trial may go ahead after 14 days from receipt of notification, if the MHRA has not raised any objections. This means that the acknowledgement letter will act as the authorisation. Further details are provided on the MHRA website.

(NB - Ethics Committee role: All interventional trials of an IMP conducted in the UK will continue to require a positive opinion from a Research Ethics Committee before they may commence),

Amendments made to the protocol during the course of a trial should be considered as the same risk category as the initial application if all else remains the same. For instance, in a Type A trial, amending the protocol within the terms of the SmPC would require no action with respect to the MHRA. However, amendments to Type B and C trials (or Type A trials beyond the terms of the SmPC) would require submission as a Substantial Amendment and approval from the MHRA before they may go ahead.

## 2. Content of the Application

For marketed medicines where there will be a significant body of data available on quality, safety and efficacy, it will usually be possible to submit much simplified documentation in support of the CTA application for a clinical trial. Examples of these simplifications in the CTD include:

### *a) IMP Dossier*

An IMP dossier (IMPD) should generally accompany each application. It gives information related to the quality of the IMP (including reference product and placebo), manufacture and control of the products, and data from non-clinical studies as well as from clinical use. This may either be provided as a stand-alone IMPD or cross-refer to the Investigator's Brochure (IB) for the preclinical/clinical parts of the IMPD. In the latter case, the summaries of pre-clinical/clinical information should include data (preferably in tables) that provides sufficient detail for assessors to reach a decision about the potential toxicity of the IMP and the safety of its use in the proposed trial. This applies to Type C trials.

Where the IMP is authorised in any EU Member State and used in the trial without any modification (including repackaging), the Summary of Product Characteristics (SmPC) may replace the IMP dossier. Where the IMP is authorised in an ICH country (USA or Japan) and is used in the trial without any modification (including repackaging), a copy of the prescriber's information (equivalent to the SmPC) may replace the IMP dossier. If this document is originally in a language other than English, an English translation should be provided. This applies to Type A and some Type B trials.

Medicinal products which have already been authorised may be modified or processed (including repackaged) to use in blinded studies. The marketing authorisation holder (MAH) of a product is only responsible for the unchanged product in its designated and authorised packaging. In other words, there is a need to ensure that the quality of the product is not negatively affected by the modifications performed. This means that modifications carried out on the authorised product should be described and their potential influence on the quality of the product discussed. In the case of a significant modification, e.g. grinding of a tablet, re-lubrication/compression, or processing with an excipient not present in the original formulation that has a likely impact on product stability, a minimum of stability data on the modified product should be available. This will allow an assessment of the impact of the modifications on product safety and stability. In the case of only minor modifications, a justification of the stability over the intended trial period provided in the protocol could be acceptable.

Where the IMP is not a licensed product, a simplified dossier may also be possible,for example, where an IMP was subject to a previously authorised CTA or where the active substance is included in a medicinal product that is authorised in an EU Member State.. However, this would be considered on a case-by-case basis.

(ref: Eudralex CT-1, 2.7.3.2, 85)

### *b) Investigator's Brochure*

A request for trial authorisation has to be accompanied by an Investigator's Brochure. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol. These key features include the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The Investigator's Brochure should be prepared from all available information/evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product (IMP) in the trial, and be presented in the format of summaries. This applies to Type C trials.

If the IMP is authorised in any EU Member State and is used according to the terms of the marketing authorisation, the Summary of Product Characteristics (SmPC) will replace the Investigator's Brochure. If the IMP is authorised in an ICH country (USA or Japan) a copy of the prescriber's information (equivalent to the SmPC) will replace the Investigator's Brochure. If this document is originally in a language other than English, an English translation should be provided. This applies to Type A trials.

When the conditions of use in the clinical trial differ from those authorised, the SmPC or equivalent should be complemented with a summary of relevant data that support the use of the IMP in the clinical trial. This can be provided as an Investigator's Brochure or, in some cases, may be incorporated into the protocol. This applies to Type B trials.

(ref: Eudralex CT-1, 2.6, 56)

### *c) GMP compliance*

The manufacture and/or assembly (packaging and labelling) of an IMP can only be undertaken by the holder of an authorisation for the manufacture of investigational medicinal products. A copy of the manufacturer's authorisation should be provided for each EU site undertaking any manufacturing step in the preparation of the test product or any comparator. This applies to Type C trials.

Where manufacture and/or assembly occur outside of the EU, the product has to be imported by the holder of a manufacturer's authorisation covering the importation activity of an IMP. A copy of the manufacturer's authorisation should be provided as part of the application. In addition, a copy of the Qualified Person (QP) declaration on GMP equivalence to EU GMP should be provided.

This requirement does not apply where the product:

- has a marketing authorisation in an EU Member State and is not modified (including repackaging)
- has a marketing authorisation in an ICH country (USA or Japan)
- is manufactured in an EU Member State and is not modified (including repackaged).

This would be the case for Type A and some Type B trials.

Additionally, this requirement does not apply where:

- packaging and/or labelling is carried out in a hospital/health centre by a doctor/pharmacist/person acting under the supervision of a pharmacist; and the investigational medicinal products are packaged and/or labelled exclusively for use in that hospital or health centre
- or any other hospital/health centre that is a site for the clinical trial in which the product is to be used.

Please note, blinding of a comparator product by over-encapsulation is classed as manufacture and is subject to the requirements above.

(ref: Eudralex CT-1, 2.7.1, 61)

## 3. Labelling

### a) *Need for trial labelling*

The application dossier submitted should contain the content of the labelling of the IMP. Labelling of an IMP is intended to:

- ensure protection of the participant and traceability
- enable identification of the product and trial
- facilitate proper use of the investigational medicinal product.

Further information on what the labelling should contain is available in section b) below. This applies to all trials, other than Type A trials.

Trial-specific labelling is not required where the IMP:

- has a marketing authorisation in the UK, and
- is being used within the terms of its marketing authorisation, and
- is dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and is labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/3194) (Marketing Authorisations Etc) Regulations 1994 that apply in relation to dispensed relevant medicinal products.

This might apply to some Type A trials.

### b) *Content of the labelling*

This section provides further information on the contents of the label, where trial-specific labelling is required (see Section a). Where the IMP does not have a marketing authorisation in the UK or where an authorised product is repackaged for the purposes of the trial, full labelling is required. The following information should be included on labels, unless its absence can be justified:

(a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding)
(b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency
(c) the batch and/or code number to identify the contents and packaging operation;
(d) a trial reference code allowing identification of the trial, site, investigator and sponsor, if not given elsewhere;
(e) the trial participant identification number/treatment number and, where relevant, the visit number
(f) the name of the investigator (if not included in (a) or (d))
(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial participant or person administering the product)
(h) "For clinical trial use only" or similar wording
(i) the storage conditions
(j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
(k) "keep out of reach of children", except when the product is for use in trials where the product is not taken home by participants

This applies to all trials, other than Type A trials.

Where the investigational medicinal product has a marketing authorisation in the UK, is being used within the terms of that marketing authorisation and has not been repackaged for use in

the trial, reduced labelling can be used. The following particulars should be added to the original container, but should not obscure the original labelling:

i) name of sponsor, contract research organisation or investigator
ii) trial reference code allowing identification of the trial site, investigator and trial participant.

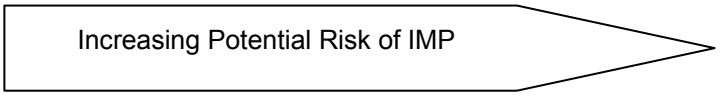
This could apply to Type A trials.

(refs: Annex 13, 32 and 2001/20/EC, Article 14, Commission Directive 2003/94/EC Article 15 SI 2001/20 Para 46)

## 4. Safety Surveillance

### *a) Adverse event recording and reporting*

For medicines where there is already a significant amount of safety data available, such as many marketed medicines, it is possible to state in the protocol that certain adverse events do not need to be reported by the investigator to the sponsor in the normal way. This proposal in the protocol will be assessed at the time of the CTA assessment by the MHRA, as either acceptable or not.This applies to Type A trials and potentially to some Type B trials.




| Are Risk Adaptions possible? | Type A | Type B | Type C |
|---|---|---|---|
| Adverse Event/Reaction Recording | Yes | (Yes) | (Yes) |
| Adverse Event/Reaction Reporting to Sponsor* | Yes | (Yes) | (Yes) |
| SAE/SAR Event Reporting to Sponsor* | (Yes) | (Yes) | (Yes) |
| SUSAR reporting to MHRA/REC/Concerned Investigators | No | No | No |
| Annual Safety Report | No | No | No |

*Yes – possible; (Yes) – may be possible on case by case basis;*
*No – little, if any flexibility in requirements; * no specific clinical trial regulatory requirements*

* Dependent upon whether sponsor or the sponsor's delegated chief investigator makes relatedness and expectedness assessment

(ref: SI 2004/1031, reg 32, (4))

### *b) Nature and extent of safety monitoring*

The nature and extent of patient safety monitoring should be based on the assessment of the risks of the trial intervention(s) relative to standard care and the extent of knowledge about the IMPs being tested. A safety monitoring plan should be developed for all trials based on an assessment of the specific risk factors associated with IMP and trial procedures, addressing those factors incremental to standard care and considering options to mitigate those risks. This is described in more detail in Appendix 2.

## 5. IMP Management

***a) Tracking and accountability processes***

In general, the further away from standard practice the trial is, the greater the record-keeping requirements.; For trials of products which have no authorisation (intended for Regulatory Submission) (Type C) and in some trials with designs markedly different from standard care (Type B), documentary evidence of a full chain of custody of IMP from supply to destruction, from which both the quantities and quality of the trial product used can be determined, will be required; ICH GCP-style records of accountability would be expected (See ICH Document E6: Good Clinical Practice section 4.6.)

For Type A and some Type B trials where it may not be possible to maintain full records of accountability, legislation and guidance does not provide a provision for this, but it will be reviewed on a case-by-case basis dependent upon other risk factors related to the trial and the level of risk associated with the trial overall. The Sponsor/Chief Investigator should ensure that the protocol makes clear what data are integral to the results of the trial, and consequently which records may be subject to a lower level of scrutiny and/or have reduced record-keeping requirements.Where it is proposed that an alternative record captures the data for drug accountability (or indeed where records may be significantly reduced), the Sponsor/Chief Investigator has a responsibility to ensure the approach is transparent and fully justified in the protocol. The following points are made to assist sponsors/researchers:

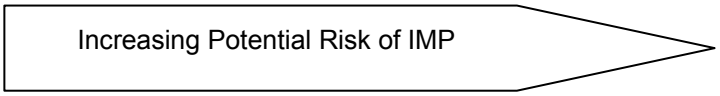
In general, measures should be in place to ascertain whether or not the trial medication was taken by the participants in the trial, as proscribed by the protocol. However, trials of authorised products with trial designs equivalent to standard care may justify simplified record-keeping dependent on the logistics of the trial conduct and the criticality of the IMP data to the analysis and the trial results.

For trials designed to determine 'real use' of products, alternative measures such as trial participant diaries and questionnaires, coupled with the pharmacokinetic or other trial measures may provide valuable data in support of the trial, rather than detailed accountability logs, which may prove impractical or even impossible to complete. Checks through discussion with the participant at follow-up visits and/or checks of medications held (including 'empty packs') may be an alternative to individual pharmacy records of drug accountability.

In the case of pragmatic trials where local provision of IMP may be hampered by complex record-keeping requirements (for example where medication is supplied through routine prescribing practices involving community pharmacies), Sponsors/Chief Investigators should give thought to the extent of information necessary for them to confirm the results and end-points of their trial, and devise relevant mechanisms on a case-by-case basis.

For trials using authorised products dispensed from the hospital pharmacy, it may be possible to maintain simplified accountability records, or to capture the batch number of the product dispensed on a standard prescription form, filing these forms in a trial folder would then permit retrospective verification if this was necessary. (In this latter case, in practical terms, the research team would need to give thought to how the pharmacy would know the prescription presented was for a trial, but a simple sticker or trial-specific prescription could facilitate this).

During GCP inspections, compliance with the provisions proposed in the protocol will be verified. It may be necessary to further clarify and discuss with Inspectors the importance and relevance of the records which are present in terms of the trial design, trial results and their completeness at the individual and trial level.




| Are Risk Adaptions possible? | Type A | Type B | Type C |
|---|---|---|---|
| Trial Level IMP Accountability | Yes | (Yes) | No |
| Subject Level IMP Accountability | Yes | (Yes) | No |

*Yes – possible; (Yes) – may be possible on case by case basis;*
*No – little, if any flexibility in requirements; * no specific clinical trial regulatory requirements*

**c) *Storage***

The Sponsor of a trial should determine acceptable storage requirements for the medicinal products used in that trial (temperatures and conditions, such as light/moisture protection etc).

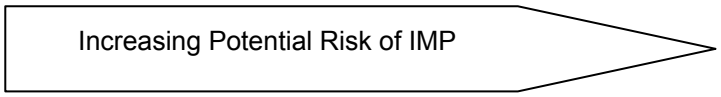
For Type C trials these must be included in the protocol to ensure all participating sites are aware of them. Furthermore, the extent of available stability data should support the extent of any proposed reporting of deviations/excursions from these requirements.

For Type A and Type B trials, storage requirements of the IMP are likely to be well known and storage in accordance with normal clinical practice will be appropriate.

In all trials, generally the more sensitive the product to deviation from the determined storage conditions, the closer the scrutiny to compliance should be. For example, where small deviations can result in marked negative impact upon the quality or activity of the product, as a minimum, daily measurements of the temperature (typically using a minimum/maximum thermometer or continuous monitoring) would be expected.

For trials with products which have been in clinical use for a long time, i.e. many Type A and Type B trials, with extensive supporting stability data, it may be possible to decide what limits are appropriate to the drug storage deviations such that deviations of short duration or small temperature fluctuations (transient changes) of little significance to the trial outcome do not need to be recorded.

In all cases, where an excursion from the expected storage temperature takes place, this should be detectable in a timely manner, before subjects are dosed, and should be assessed in terms of the impact on the medication quality. This documented assessment would be made in terms of the impact on the effectiveness of the medicine and the consequences on the trial results and patient safety.




| Are Risk Adaptions possible? | Type A | Type B | Type C |
|---|---|---|---|
| Storage Conditions Records | (Yes) | (Yes) | No |
| Deviation Impact Assessment | (Yes) | (Yes) | No |

*Yes – possible; (Yes) – may be possible on case by case basis;*
*No – little, if any flexibility in requirements; * no specific clinical trial regulatory requirements*

## 6. Documentation

### *a) Trial Master File (TMF) Content*

For all trials (Types A, B and C), the TMF must contain sufficient information in their trial files to comply with Regulation 31A .The extent of documentation is open to interpretation. A commonly used framework is described in ICH GCP E6 Section 8, particularly sections 8.2 to 8.4, and guidance on the TMF and Archiving is provided in Volume 10.for Clinical Trials. It has become common proactice for monitors, auditors and inspectors to review trial files against these standards. However, ALL documents which enable the conduct, quality and compliance of the clinical trial to be verified should be retained. As a result, any examples of impact on documentation provided in this paper are not intended to give a comprehensive list of all documentation that may be generated during a trial conducted at a particular organisation.

Risk adaption of the Trial Master File documents (, as defined in Volume 10 Guidance, ICH GCP E6) may include:

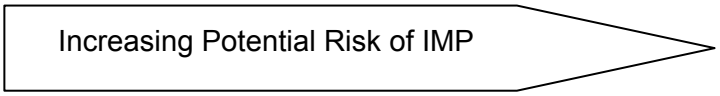
- **Replacement** by a document that serves a similar function, but does not carry the title presented in ICH GCP E6 Essential Documents*.
- **Combining of documents** so that one document serves a number of purposes
- **Removal**, or not present because it is no longer applicable as a result of implementation of other risk adaption measures

*Note: under the UK regulations (SI 2004:1031 as amended Regulation 31A), these documents are still 'essential' – an essential document is defined as any document needed to enable the conduct, quality or compliance to be verified.

The tables below summarise the impact on the trial documentation from the adaptions currently permitted by the Clinical Trials and GCP Directives that have been presented in the text **as examples**. Further guidance on TMF documentation will be made available via the MHRA website and this will be revised and developed as the use of risk-adaption becomes more widespread, for example, impact of risk adaptation on clinical trial monitoring and the resultant documentation.

**Risk-adaption Related to the IMP**

*Documents described in ICH Essential Documents*




| **Document**<br>**Are Risk Adaptions possible?** | **Type A** | **Type B** | **Type C** |
|---|---|---|---|
| Investigators Brochure (IB) | Yes | (Yes) | No |
| IB annual Update† | No | No | No |
| Sample Label | Yes | (Yes) | No |
| Certificate(s) of Analysis | Yes | (Yes) | No |
| Investigational Medicinal Product (IMP) Shipment(s) | Yes | Yes | No |
| Instructions for Handling IMP(s) | Yes | (Yes) | No |
| Master Randomisation List‡ | No | No | No |
| Decoding Procedures for Blinded Trials | No | No | No |
| IMP Accountability at Site | Yes | (Yes) | No |
| IMP Return &/or Destruction | Yes | (Yes) | No |

Additional documentary considerations resulting from the Directive:

(included here for completeness, details are included further in the Joint Risk Project proposals)

*Documents described in Directive 2001/20/EC &/or Directive 2005/28/EC*

| **Document**<br>**Are Risk Adaptions possible?** | **Type A** | **Type B** | **Type C** |
|---|---|---|---|
| Investigational Medicinal Product Dossier | Yes | (Yes) | No |
| Manufacturer's Authorisation for Investigational Medicinal Product (MIA (IMP) | Yes | (Yes) | No |
| Manufacturer's Authorisation (MA) | (Yes) | No | No |
| Authorisation for IMP Importation | No | No | No |
| Qualified Person Certification<br>(where required) | Not Applicable | (Yes) | No |
| Statement of EU GMP or EU GMP Equivalence | Yes | (Yes) | No |

*Yes – possible, (Yes) – may be possible on case by case basis,*

*No – little, if any flexibility in requirements*

† Requirement conferred by Directive 2005/28/EC not ICH GCP

‡ Note for all trials where randomisation and/or blinding takes place it should be documented how this procedure was undertaken in order to verify compliance with the randomisation schedule

It should be borne in mind that the presence of a placebo within a trial design, may mean additional documentation is required for Type A and Type B trials to demonstrate the quality of that product (the placebo) has been maintained and that the requirements of GMP have been satisfied.

**Risk-adaption Related to Safety Surveillance**

For safety surveillance and reporting, the requirements and permitted adaptations are the same for all categories of trials

| **Document**<br>*Documents described in ICH Essential Documents* | **Adaption Possible** |
|---|---|
| Safety Surveillance<br>(as described in the protocol) | Yes |
| Serious Adverse Event Reports | Yes |
| Adverse Event Reports | Yes |

Additional documentary considerations resulting from the Directive:
(included here for completeness)

| **Document**<br>*Documents described in Directive 2001/20/EC &/or Directive 2005/28/EC* | **Adaption Possible** |
|---|---|
| Additional Information Relating to Death Reports | No |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports | No |
| Evidence that Concerned Investigators have been informed of SUSARs for the IMP | No |
| Annual List of Suspected Serious Adverse Reactions as part of the Annual Safety Report/Drug Safety Update Report | No |

Additional documentation resulting from the Risk-adaption Proposals:

| **Document** | **Type A** | **Type B** | **Type C** |
|---|---|---|---|
| Safety Monitoring Plan | No | No | No |

This document is anticipated to be highly adapted to the trial under consideration, consequently for trials in marketed products used within their authorisation, it is anticipated that this plan will not be extensive unless the intervention/normal treatment regime is complex.

**Examples of Essential Documents that May be Adapted by Combination**

There are a number of essential documents which it may be possible to adapt by combining them. Typically such documents include staff delegation, and signature logs which specifically assign the responsibility of Case Report Form corrections and/or subject identification, screening and enrolment logs.

For research active centres, it may be appropriate for records to be held centrally rather than in each trial, in order that they may be referenced by a number of trials, and maintained, controlled and updated in a co-ordinated manner periodically, rather than each time a trial is established. Such records may include curriculum vitae, statements of GCP training, definition of clinical trial responsibilities by role (where those assigned to each role is then further included in the trial-specific record), records that demonstrate equipment (including computerised systems), facilities or storage areas are fit-for-purpose and/or normal values (such as laboratory ranges).

All trials categories may have records that are adapted in this way. It is anticipated that such arrangements would be transparent in Standard Operating Procedures.

**A Combined Trial Master File/Investigator Site File**

Where extensive functions/tasks have been delegated from the Sponsor to the Investigator, the Trial Master File and Investigator Site Files may be combined. Consequently the Investigator *may* assume responsibility for maintenance of a number of the records ICH defines as the responsibility of the Sponsor. Under these circumstances, there is no requirement for the separate maintenance by the Investigator of both a Trial Master File and an Investigator Site File.

Due consideration should be given to the confidentiality of personal data in line with national data protection requirements and the undertakings of the signed, informed consent.

The location of all files that constitute the Trial Master File (or combined TMF/ISF) should be referenced and retained for the total archive period in a co-ordinated manner.

Where functions of the Sponsor have been contracted to a third party, the contract (or other trial-related documentation) should specify for the establishment, maintenance and archiving of the Trial Master File.

### *b) Retention time of essential documents*

For trials that are not intended to support Marketing Authorisation applications (or variations) to the Competent Authority, the Sponsor and the Chief Investigator shall ensure that the documents contained, or which have been contained, in the TMF are retained for 5 years after the conclusion of the trial. This will apply to many of the lower-risk trials. In addition, the Sponsor and the Chief Investigator shall ensure that the medical files of trial participants are retained for at least 5 years after the conclusion of the trial.

For trials intended to support Marketing Authorisation applications (or variations) to the Competent Authority, the Marketing Authorisation Holders must arrange for essential clinical trial documents (including case report forms) other than participant's medical files, to be kept by the owners of the data:

- for at least 15 years after completion or discontinuation of the trial,
- or for at least 2 years after the granting of the last marketing authorisation in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- or for at least 2 years after formal discontinuation of clinical development of the investigational product.

(ref: DIRECTIVE 2005/28/EC, Article 17; DIRECTIVE 2003/63/EC,)

## 7. GCP Inspections

GCP Inspections have always included a risk-based element to them, but this has historically related to the number and nature of trials conducted, the extent and vulnerability of the populations included in those trials, and any prior inspection history.

Inspections are usually performed on a systems basis at the organisational level, and although trials equivalent to standard of care have been included, in general trials selected for inspection are:

- Double-blind and/or randomised in nature
- Multi-centre
- Representative across diverse therapeutic areas and subject populations

For each organisation to date, in order to evaluate the Sponsor's control and efficiency of their quality system, it has been typical to select a number of trials for review. Where possible, the focus is on the more complex trials, but where necessary including those equivalent to standard care to evaluate the system.

In some circumstances, this has resulted in a large number of findings, as trials were inadequately documented for retrospective reconstruction. Also, in the absence of clear protocols and/or comprehensive risk strategy documentation, it has not been possible (often in conjunction with the Sponsor and research team) to resolve compliance matters in terms of the significance of findings relative to the participant safety and/or trial results.

It is anticipated by Inspectors that through the introduction of a transparent risk assessment process (as described in this documentation), trials which are equivalent to standard care will be evident in the Sponsor's portfolio and will be subject to a lower frequency of inspection than those which fall at the higher end of the risk. It is likely that those organisations who conduct trials only equivalent to standard of care may not be routinely selected for inspection and/or subject to inspection on a less frequent basis.

In order for this system to function effectively, the basis of risk assessment needs to be transparent. Consequently, the MHRA GCP Inspectorate has been involved in the development of these proposals and endorse the approach described below. The GCP Inspectorate supports the outputs and will consider these in the scheduling of inspections.

Furthermore, during inspections, considerations of the Inspectors will be influenced by these proposals regarding available documentation and the extent of any systems used within the trial.

# Appendix 2

# Guidance on Risk-Proportionate Approaches to the Management and Monitoring of Clinical Trials

## Introduction

The purpose of this guidance is to assist Investigators and Sponsors:

- Consider and identify the main hazards inherent in a clinical trial protocol
- Develop relevant risk-mitigation plans
- Develop proportionate trial management and monitoring plans.

The guidance includes the assessment of risks to the safety and rights of the trial participants, and the risks to the reliability of the trial results associated with the design, data collection, and analysis. ***It does not address risks associated with the training and experience of the trial team, host sites or other institutions involved in the conduct of a study. For guidance on these aspects, see the NIHR Research Support Services Framework.***

It is recommended that the assessment of risks in a study is first undertaken in advance of an application for funding and in parallel with the development of a detailed protocol. This will allow the study design, risk mitigations*, safety monitoring procedures and trial management plans included in the protocol to be informed by the risk assessment; the extent of safety and data monitoring will also have implications for the funding and resources required. It is, therefore, recommended that critical study considerations are assessed prior to funding and sponsorship applications, as well as prior to finalisation of the study protocol.

Key objectives of this process are to:

- Provide a common language for, and structured approach to, risk assessment, trial management and monitoring planning that will facilitate discussions between stakeholders, including investigators, sponsors, funders, regulators, pharmacists, and site regulatory and governance staff.
- Achieve agreement of the regulatory authority on the level of risk associated with the trial intervention and the proposed plan for monitoring participant safety (through submission of a safety monitoring plan).
- Assist investigators in planning the resources required for the appropriate management of the study.

It is recommended that the risk assessment is re-visited periodically over the life-time of a trial to take into account new information and issues that become apparent only after the start a study.

[DN Footnote]* By risk mitigations we mean strategies or procedures that reduce either the impact or the probability of an adverse consequence of a hazard

## Risk assessment

This is considered in two sections:

A. Risks to participant safety associated with the IMPs and other intervention(s) being tested
B. Other risks associated with the design and methods of the trial, such as risks to:
    - participants due to the clinical procedures specified by the protocol;
    - participant rights related to consent and protection of their data; and
    - reliability of trial results.

## A. Risks to participant safety associated with the intervention(s) being tested

As outlined in the main document above, the risks to participants associated with the intervention(s) under investigation are assessed in relation to standard care for the patient group concerned and the level of knowledge of the effects of the interventions. The risk category of the trial interventions will guide the nature and extent of patient safety monitoring that will be required in the trial. In general a Type A trial will involve a low intensity of safety monitoring, a Type B trial a moderate intensity and a Type C trial a high intensity above standard of care. The points to consider in developing a safety monitoring plan are:

- the nature of the IMP,
- the potential toxicities (known/unknown) i.e. hazards
- which body systems may be affected
- and what monitoring will be done and when i.e. mitigation

It is suggested that the chief investigator's/sponsor's assessment of the IMP risk category and a safety monitoring plan are included with the application for a Clinical Trial Authorisation (CTA) , either as an appendix to the trial protocol, or incorporated into the body of the protocol or in a covering letter. They would thereby be reviewed by the MHRA assessor and agreed as acceptable (or not) through the MHRA response notification.

For example, a table such as this could be used to help develop the protocol and may be submitted with the CTA application:

| **Study Title:** | | | | | |
|---|---|---|---|---|---|
| **EudraCT:** | | | | | |
| **Sponsor:** | | | | | |
| **Risks associated with trial IMP/interventions**<br>☐ **Type A ≡** Comparable to the risk of standard medical care<br>☐ **Type B ≡** Somewhat higher than the risk of standard medical care<br>☐ **Type C ≡** Markedly higher than the risk of standard medical care | | **Justification** | | | |
| **IMP/Intervention** | **Body System** | **Hazard** | **Likelihood (L,M,H)** | **Mitigation** | **Comments** |
| ABC 123 | metabolic | hyperglycaemia | L | blood glucose monitoring | X hourly |
| | GIT | pancreatitis | L | amylase and lipase | daily |
| | GIT | raised transaminases | H | LFTs | daily |
| | CVS | prolonged QT interval | M | digital ECG, Holter monitoring | X Hours<br>X hours |
| **Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review,...)** | | | | | |

Measures and controls where the risk of the intervention is considered to be comparable to standard care (i.e. Type A) need not be spelled-out in detail. However basic assumptions about routine monitoring and consideration should be summarised as part of the justification provided.

**Some issues to be considered in the assessment (this list is not comprehensive)**

- Phase of development
  - Study population: healthy subjects or patients?
  - If licensed, is it being used outside its licensed indication? Has the dosage regimen/route been modified?
  - If so, what are the implications of any modifications for participants?

- Safety profile –
  - What are the known/anticipated safety issues? Are they addressed within normal clinical practice (standard care)?
  - If unknown, what are the anticipated risks/other effects based on preclinical data or knowledge of class of drugs?
  - Is the duration of use compatible with previous experience?
  - Is there a potential risk of dosing errors?

- May concomitant medications increase the risk, i.e. interactions?

- What are the implications of the status of the product for patient safety monitoring in addition to standard care e.g. additional laboratory investigations; ECG; imaging;

- Are any other risk mitigation strategies are necessary, such as
  - Restrictive eligibility criteria, e.g. exclusion of individuals at particular risk of harm because of co-morbidities or taking certain drugs which may interact
  - Treatment protocol, e.g. timing / titration of doses; location of administration (specialist unit, routine clinical setting, self-administration); therapeutic drug monitoring availability of rescue medication and, where appropriate, suitable support facilities
  - Criteria for stopping or modifying study treatment, e.g. local clinical review and decision-making; a pre-specified treatment algorithm; or central oversight of clinical safety data by dedicated trial physicians or an independent Data Monitoring Committee
  - Adverse event (AE) reporting strategy, e.g. Adverse event recording may be extensive (all AEs regardless of relatedness or seriousness or expectedness) or may be more focussed (e.g. organ-specific events, events of particular concern, or serious AEs only); although reporting to the sponsor and regulatory authority should always be in line with regulatory requirements
  - Duration of exposure and follow-up, e.g. for trials involving an advanced therapy medicinal product the duration of exposure and intensity/length of follow-up would need to be discussed
  - Trial oversight: e.g. central clinical team may be able to provide study- and drug-specific expertise; the Trial Steering Committee may include experts in the disease, its routine management and the study treatment; an independent Data Monitoring Committee to allow unblinded evaluation of emerging safety data, assessment of risk/benefit, and refinement of protocol to address any new safety concerns

## B. Other risks associated with the design and methods of the trial

This section covers those risks that arise from the protocol and study procedures, other than those associated with the intervention, namely:

1) risks to participants associated with
   a) the clinical procedures specified by the protocol;
   b) failure to obtain fully informed consent;
   c) failure to protect personal data; and

2) risks to the reliability of results

A similar process is suggested for all these areas of risk:

- Review the protocol to identify whether or not it contains any aspects that materially increase the risks in areas outlined below.
- Identify the specific potential hazards , and
- For each hazard identified, consider the appropriate mitigation, management and optimal monitoring strategy.

A table such as this might be compiled:

| **Risk Area: (see issues to be considered below)** | **Particular risk identified? (Yes/No)** | **If yes, specify concerns** | **If yes, can the risks be minimised? Specify any mitigations/ Adaptations** | **If yes, could monitoring methods help to address concerns? (Specify)** |
|---|---|---|---|---|
| | | | | |

**1. RISKS TO PARTICIPANTS**

### *a) Risks to participant safety from clinical procedures specified by the protocol*

Just as for the risks associated with the trial intervention, these should be assessed relative to standard investigations and procedures for the clinical condition of the participants in the trial. For example, if an invasive procedure (such as a biopsy) is normal practice for good quality care, then its inclusion in the study protocol would not be an additional risk to participants. However, if it was being done only for the trial and was not part of standard care then it would constitute an additional risk.

**Some issues to be considered in the assessment (this list is not comprehensive)**

- Does the protocol require any investigations or other clinical procedures that carry significant risk?
- Does the protocol require additional procedures over and above those which would be expected from standard care for the participant's clinical condition – e.g. blood tests, biopsies, X-rays, lumbar puncture, contrast media scans?
- If so, what is the likelihood and severity of the harm that might be caused to the participant?
- What measures might reduce either the likelihood or severity of harm to the study participants? For example:
  - qualifications, experience and training of clinical staff at site,
  - special facilities or equipment,
  - additional training by the CI or delegate,
  - monitoring to identify problems and take measures to protect current and future participants

### *b) Risks to participant rights from failure to obtain appropriate consent*

The ability of trial participants to give fully informed consent depends on: (i) the vulnerability and mental capacity of the study population, and (ii) the consent process. If there is some reason that the relevant study population may lack the capacity to give fully informed consent (such as being a child, having some degree of cognitive impairment or being recruited with an acute life-threatening condition or following the administration of opiate analgesics), then there might be particular concerns that may have implications for the consent process (e.g. numbers of stages or timing) and the provision of patient information according to their capacity to understand it. Detailed guidance is provided by the National Research Ethics Service (See http://www.nres.npsa.nhs.uk/applications/guidance/consent-guidance-and-forms)

The risks should be judged relative to the ability of a fully competent adult with a chronic, non-life-threatening condition to give consent.

The level of risk may also depend on the treatment options for that patient group. Where the interventions under investigation and the protocol management are similar to standard practice, the risk to patient rights in relation to receiving trial treatment would probably be judged to be lower than if experimental treatments were being tested.

Trials involving patients who are competent to give consent, but the trial intervention must be administered immediately, such that patients have very little time to consider whether or not they wish to participate may be of concern. In this instance, the effect of the time constraints on participants should be considered in both the protocol and risk management plans. In an emergency situation, the consent may have to be taken by someone, such as an A&E staff member, who is not entirely familiar with the trial.

**Some issues to be considered in the assessment (this list is not comprehensive)**

- Does the study population include particularly vulnerable groups (e.g. children, elderly, patients with mental health problems)?
- Are the participants likely to lack capacity to give fully informed consent (e.g. severe pain, cognitive impairment, language difficulties)?
  - If so, what are the foreseeable risks/burdens for these participants
- Who will decide whether or not a participant is capable of giving consent?
- Does the consent process allow sufficient time for the participants to consider their decision and discuss it with an independent party (e.g. non-emergency treatment)
- What measures might reduce the likelihood that participants might be included in the study without the appropriate level of consent? For example:
  - experience and training of clinical staff at site,
  - nomination of a professional representative, legal representative or consultee
  - assent guidance
  - additional training by the CI or delegate,
  - monitoring to identify problems and take measures to protect current and future participants

### *c) Risks to participant rights from failure to protect their personal data*

It is essential that personal data collected in the course of any clinical study, even if collected with the consent of the individual, are held securely and are only accessed by authorised staff. There may be particular concerns for the preservation of participant confidentiality, where the data in question are especially sensitive or when the study involves the transfer of data between organisations (see the Framework Code of Practice provided by the Information Commissioner's Office).

**Some issues to be considered in the assessment (this list is not comprehensive)**

- Are particularly sensitive data being collected?
- Are personal identifiers associated with the data?
- Will consent of the participant to access and use the data been obtained? If personal consent is not possible, has consideration been given to what would happen to the data in the event that the patient dies?
- Are data to be sent outside the country? Are data protections equivalent to those in the UK?
- Has consent been given to share the data with third parties (if relevant)?
- Are the data security measures appropriate to the types of data?

## 2. Risks to the reliability of results

The design of a study has a major impact on the robustness of the results. The objectives of a study may limit the design options and render some features of a robust design inappropriate. For example, in an early phase trial of a drug about which there are serious safety concerns, detailed eligibility criteria may well be required, whereas they may be an inappropriate obstacle to obtaining reliable general evidence in a pragmatic trial of an intervention that is in common use. A subjective outcome may be the relevant endpoint for a trial, but it may be difficult to mask the identity of the intervention from the persons assessing the outcome, thus increasing the risk of bias. In general, the more robust the design the less the dependence there is on quality control and assurance measures to secure reliable results. Within the constraints imposed by the objectives of the trial, the investigators are advised to make the study as robust as possible. Obstacles to recruiting sufficiently large numbers of patients in order to assess the efficacy and safety of the study treatment reliably should also be identified and, wherever possible, mitigated.

***Features of a robust design include:***

- Simple, relevant eligibility criteria
- Outcome measures which are objective and simple to assess accurately.
- If objective outcome measures cannot be used, then effective masking of the intervention when assessing the outcome
- A properly generated randomisation schedule and a randomisation method that prevents the prediction of treatment allocation when entering patients into the trial
- A simple intervention that is difficult to apply incorrectly
- Sufficient power to detect realistic effects of the intervention
- Minimal risk of missing key data items, for example, by having a short follow-up or a follow-up schedule that is similar to standard care

The Cochrane Risk of Bias Tool provides additional guidance on these issues (http://cdag.cochrane.org/Files/risk%20of%20bias%20table%20template.doc).

It is important to recognise that it is the reliability of the trial results rather than the data *per se* that is paramount. So quality control and assurance methods should focus on the quality of data required to meet the trial objectives and obtain reliable results rather than simply on data accuracy. In particular, randomised controlled trials have strengths, e.g. a control group that differs only randomly from the intervention group - other than with respect to the effects of the investigational treatment that may allow differences in outcome to be assessed reliably. This may be possible even when data collection is not complete, provided that data quality does not differ systematically by treatment group. Even so, it is appropriate that investigators and sponsors put in place systems that facilitate the collection of data that are of sufficiently good quality for the purposes of the trial, and to justify the approaches that they have taken. For example, it may be appropriate to undertake targeted quality control of key items (e.g. endpoint data) and to tolerate some variability in the quality of some other data items.

***Data collection and handling methods that may help improve data quality include:***

- well-designed, unambiguous and tested case report forms (CRFs), whether paper or electronic, that focus on the essential data required for the particular trial
- procedures to ensure a timely flow of data from investigator sites and checks of the data, as they are received
- a user-friendly, validated database
- data verification and validation (e.g. a database may contain in-built range and consistency checks)
- data management and transfer methods that ensure an audit trail is maintained from the primary data to the database, and from the database to the analysis files (with changes that are controlled, attributable, and properly authorised).
- valid analyses using appropriate techniques; this may be facilitated by the development of a statistical analysis plan that is peer-reviewed and agreed with the trial oversight committees
- quality control checks of statistical outputs (and publication)

***Some issues to be considered in the assessment (this list is not comprehensive):***

**(i) Robustness of the trial design**

- Eligibility criteria:
  - Compl exity
  - Special tests/assessments required
  - Potential for external verification
  - Degree of precision required for trial validity

- Method of randomisation (if applicable):
  - Robust method used to generate and check the randomisation schedule
  - Does the method of random allocation of treatment arm prevent prediction before a patient is entered into the trial? For example, centralised randomisation by telephone or web; by allocation of a treatment pack held in pharmacy rather than sealed envelopes stored in clinic; avoidance of known block sizes, particularly in an open label study

- Intervention:
  - Complexity/potential for error (e.g. complex chemotherapeutic regimen with multiple drugs, different doses and dose-adjustments)
  - Clarity of process of dose escalation (if applicable)
  - IMP management, storage and dispensing requirements
  - Impact and likelihood of non-adherence

- Masking of the intervention (if applicable):
  - This is always desirable if it can be achieved, but is it essential? For example, outcome measures cannot be objective
  - Who needs to be blinded? For example, patient, clinician, clinical assessor
  - Is it effective? Has it been tested? Could there be any unwarranted unblinding in the course of the trial?
  - Could there be any unblinding during the course of the trial? Consider potential impacts of who has access to randomisation schedule, methods for emergency unblinding, unblinding for Serious Unexpected Suspected Adverse Reaction reporting, whether unblinding of individual patients' treatment will be required before the end of the trial

- O utcome measures:
  - Degree of objectivity
  - Potential for standardised assessment with validated methods
  - Potential for simple external verification (e.g. death certificate, copy of an investigation report)

- Potential for unbiased adjudication or review (masked to treatment allocation – e.g. Central assessment of investigations, Independent Endpoint Review)

- Completeness of follow-up:
  - Duration
  - Intens ity
  - Complexity of procedures – extent to which they differ from normal care of the patient group
  - Impact and likelihood of non-adherence

- Statistical issues all considered, such as:
  - Clear objectives and endpoint measurements
  - Appropriate trial design
  - Adequate sample size (e.g. is there sufficient power to comfortably detect the anticipated effect of the intervention)
  - Clear and appropriate analysis plans (interim and final)

**(ii) Data collection methods**

- Volume and complexity of the data required
  - Including amount and required timeliness of patient safety data
- Design and piloting of the CRF
- Database design, validation and testing
- Potential for fraudulent data and for detection via the database
- Methods of data transfer from primary data to database to final analysis file

**(iii) Site issues (**NB these are not fully addressed in this guidance – see NIHR Research Support Services Framework for further details**)**

- May there be sites included in the trial that introduce particular vulnerabilities, such as inexperienced sites or sites where there may be language barriers?

## Risk-adapted trial monitoring plans

Trial monitoring is not a standardised activity that must be implemented in an identical way in all trials. The risk assessment guidance in this paper is designed to assist sponsors and investigators in the identification of the main risks in the trial, and the development of targeted and proportionate monitoring plans. Following a structured review of the vulnerabilities associated with the trial design and methods, as suggested above, a trial-specific and targeted monitoring plan may be developed. However, unanticipated risks may emerge in the course of a trial; it is therefore recommended that the risk assessment and associated monitoring plans be kept under review and modified as necessary.

The purpose of trial monitoring is to provide oversight during the conduct of a trial to give reassurance that the study protocol and procedures are being followed, that and legal/governance requirements are being complied with, and that the critical data collected are reliable. If they are not, these need to be identified in a timely way so that remedial actions can be taken (for example, further training). Conducting a risk assessment should identify the main potential risks associated with a trial protocol, and lead to the selection of appropriate management and monitoring approaches to mitigate those risks and to indentify and resolve issues promptly.

The extent and nature of monitoring would normally be determined prior to the start of the trial and be re-assessed during the course of a trial. The clinical trial risk assessment may be used to determine the **intensity** and the **focus** of the monitoring activity, whilst the trial design would inform the **methods** used for monitoring. Assessment of the sites, staff facilities and training needs may also influence the intensity and nature of monitoring methods.

There are a number of different approaches and techniques that are commonly used for study monitoring (see below). However, there is little empirical evidence on their effectiveness and optimal use. On the basis of experience, it is reasonable to select some or all of them for inclusion in study monitoring plans. Which approaches are used will depend on the nature of the risks identified for a trial and their potential impact. Further research is needed on the efficacy and cost-effectiveness of different procedures so that future decisions on monitoring can be evidence-based.

## 1. Commonly used monitoring procedures

Commonly used monitoring procedures which are described in more detail in the Clinical Trials Toolkit (http://www.ct-toolkit.ac.uk/_db/_documents/Trial_MP.pdf) include:

- Trial oversight structures, for example:
  - Trial Management Group (TMG)
  - Trial Steering Committee (TSC)
  - Independent Data Monitoring Committee (IDMC)

- Monitoring activities that do not require visits to individual sites, for example:
  - Monitoring trial progress from the coordinating centre by the trial team
  - Resolving trial-related issues by telephone/email
  - Ongoing training/motivation meetings and teleconferences
  - Telephone conversations with site staff, web-enabled training

- Central monitoring of the trial and data, for example:
  - Eligibility checks prior to randomisation
  - Rates of recruitment, withdrawals and losses to follow-up by site
  - Checks for missing or invalid data (range and consistency checks)
  - Checks that dose adjustments, investigation and management of events are consistent with the protocol
  - Cale ndar checks
  - Checks for unusual data patterns
  - Assessment of adverse event and toxicity reporting rates
  - CRFs completed by authorised persons
  - External verification (with participant consent) of events (e.g. birth, disease and death registries)

- On-site monitoring visits:
  - Ongoi ng training/motivation
  - Checking understanding and adherence to study protocol, procedures and governance requirements (including any conditions in regulatory or ethics approval)
  - Review of consent procedures
  - Source data verification (as appropriate for the particular trial)
  - Verification that resources and facilities remain adequate
  - Verification of appropriate oversight and documented delegation by the local investigator

The impact of problems identified during the course of a trial should be considered at the level of both the individual trial participants and the overall trial results. Robust monitoring procedures should allow appropriate moderation or escalation of issues, dependent upon the outcome of the measures employed. For example, for a site where remote monitoring or central monitoring is not resulting in improved data quality, site visits may be appropriate. Any action taken in response to monitoring should be evident in the records for the trial maintained by the site, trial coordinating team, and/or sponsor.

## 2. Guidance on the focus and intensity of monitoring

The chart below brings together the risk assessments described above, and provides principles for investigators and sponsors to consider when determining the focus, type and intensity of study monitoring. There are many different approaches to quality control in a clinical study, and the most appropriate modalities will depend on the number of sites and logistical issues as well as the risk.

| | | **Concerns identified in the assessment of risk associated with the design, methods or conduct of the trial (other than the intervention) which remain after mitigations are in place** | |
|---|---|---|---|
| | | **No** | **Yes** |
| **Risk associated with the intervention /IMP** | **Type A** | **Low intensity**<br>Central monitoring of protocol adherence and data quality. No requirement for site visiting unless there are concerns identified from central monitoring that cannot be addressed by other means | **Low+**<br>As outlined in A, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment. |
| | **Type B** | **Moderate intensity**<br>Central monitoring of safety data quality and timeliness as well as protocol adherence and quality of other trial data.<br><br>Triggered visits for poor data return or protocol adherence concerns as well as unusually low or high frequency of Serious Adverse Events (SAE) reports (for studies where between-site comparisons are possible). | **Moderate+**<br>As outlined in B, plus appropriate monitoring appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment. |
| | **Type C** | **Higher intensity**<br>More intense monitoring than above to have confidence in the completeness and reliability of safety data | **Higher+**<br>As outlined in C, plus appropriate monitoring to address the specific vulnerabilities associated with trial design, methods or conduct identified in the risk assessment. |

The level of risk of the intervention relative to the standard of care for the condition in question may influence the intensity of monitoring and lower the threshold for site visits. In general, the less clinical experience there is with a treatment, the greater the importance that safety data are complete and the lower the threshold might be to visit a site where data quality is in question. For trials using unlicensed IMP (Type C), GCP inspectors would usually expect effective site visits to be part of the monitoring plan.

Where central monitoring methods predominate, for example in Type A trials with no particular trial design vulnerabilities, there may still be reasons for site visits or other direct contact with site staff, when central monitoring indicates a cause for concern or for other reasons (such as new sites that are less well known to the trial coordinating team or when there have been changes of key site staff).

Whatever the monitoring plan, the results of the monitoring (by whichever methods employed) should be used to inform necessary changes to the trial management and monitoring plans. They may justify moderation (downgrading of activities) or require escalation of activities to correct a problem or prevent it reoccurring (for example, additional training and revised processes).

# Appendix 3 - Membership of the Ad-hoc Working Group and Risk-stratification Sub-group

## Ad-hoc Working Group

### Co-Chairs

| | |
|---|---|
| Professor Janet Darbyshire | Director, Clinical Trials Unit, Medical Research Council |
| Professor Kent Woods | Chief Executive, MHRA |

### Academia/Research Network

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| Gillian Booth | CTRU, Leeds University |
| Professor Julia Brown | CTRU, Leeds University |
| Viv Brown | Director, CCRN Delivery, NIHR CRN |
| Professor Stephanie Burns | NIHR Mental Health Research Network |
| Professor David Cameron | NIHR Cancer Research Network, Leeds University |
| Professor Sir Rory Collins | CTSU, Oxford |
| Professor Gary Ford | NIHR Stroke Research Network, Newcastle University |
| Dr Jonathan Gower | NIHR CCRN |
| Fiona O'Neill | NIHR CRN |
| Jesus Perez | Head of East Anglia Hub, NIHR Mental Health Research Network |
| Professor Martin Rossor | Director of NIHR DeNDroN, UCL |
| Professor Steve Smye | Director of NIHR CCRN |
| Professor Paul Stewart | Birmingham University |
| Peter Stonier | Faculty of Pharmaceutical Medicine, Liverpool University |
| Paul Wallace | NIHR CRN |
| Professor Tom Walley | HTA and Liverpool University |
| Hywel Williams | Nottingham University |
| Professor Paula Williamson | Director of NIHR Medicines for Children CTU, |
| Professor Til Wykes | NIHR Mental Health Research Network, King's College, London |

### Cancer Research UK

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| Peter Johnson | Chief Clinician |
| Kate Law | Director of Clinical Research |

### Department of Health

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| Robin Banjeri | Head of Communications, NIHR |
| Marc Taylor | Deputy Director, R&D Systems and Governance |
| Glen Wells | Research and Development Directorate |

### Medical Research Council (MRC)

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| Dr Catherine Elliott | Research and Training |
| Dr Sarah Meredith | Clinical Epidemiologist, MRC Clinical Trials Unit |

### Medicines and Healthcare Products Regulatory Agency (MHRA)

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| Brian Davis | Consultant to MHRA on Clinical Trials Work |
| Andy French | Group Manager, Licensing |
| Simon Gregor | Director of Communications |
| Rebecca Harrison | Group Manager, Inspections |
| Gerald Heddell | Director of Inspection, Enforcement and Standards (IES) |
| Ian Hudson | Director of Licensing |
| Maggie Jackman | Head of Strategy and European Medicines Agency |
| Aidan McIvor | Office of the Chief Executive |
| Chris McEwan Polic | y Division |
| Louise Mawer | Senior GCP Inspector |
| Jonathan Mogford | Director of Policy |
| Martyn Ward | Head of Clinical Trials Unit |

## Membership of the Risk-Stratification Sub-Group

### Co-Chairs:

Sarah Meredith, MRC Clinical Trials Unit
Martyn Ward, MHRA Clinical Trials Unit

### Members:

Gillian Booth, Clinical Trials Research Unit, Leeds
Carrol Gamble, NIHR Medicines for Children Research Network Clinical Trials Unit, Liverpool
Heather House, University of Oxford & Oxford Radcliffe Hospitals NHS Trust
Martin Landray, Clinical Trial Service Unit, University of Oxford
Louise Mawer (Replaced by Andrew Fisher in 2011), MHRA GCP Inspectorate
Wilma van Riel, Birmingham Clinical Trials Unit