

An initial pilot assessment of the MHRA risk-adapted approaches to the management of clinical trials of investigational medicinal products

1. Executive Summary

- 1.1. The NIHR Evaluation Trials and Studies Co-ordinating Centre (NETSCC) undertook a pilot of the new Medicines and Healthcare Regulatory Authority (MHRA) guidance resource entitled 'risk adapted approaches to the management of clinical trials of investigational medicinal products' in early 2011.
- 1.2. Pilot participants included funded HTA and EME programme clinical trial project teams, Clinical Trials Units and NHS Trust R&D offices.
- 1.3. The majority of participants thought the MHRA guidance was valuable and timely. However some concern was expressed about the overall process, in particular in terms of length, complexity and clarity.
- 1.4. Recommendations for modifying the guidance typically focused on the need for greater clarity and improved structure.

2. Introduction

- 2.1. NETSCC was asked to undertake a pilot of the MHRA guidance resource entitled 'risk-adapted approaches to the management of clinical trials of investigational medicinal products' by Professor Tom Walley (Director of NIHR Evaluation, Trials and Studies) in early 2011.
- 2.2. The MHRA developed the guidance resource as part of a NIHR/MHRA/MRC-CTU joint project. The work was undertaken as a response to a growing requirement to adopt a more relaxed approach to clinical trials activity and GCP requirements undertaken by non-commercial sponsors. Its implementation and use by researchers is intended to facilitate a risk-proportionate approach to the management and monitoring of clinical trials. A copy is provided for reference in Appendix A.
- 2.3. This report has been created for the use of the MHRA, NIHR and other partners associated with the guidance resource development and implementation activities.

3. Background

- 3.1. The implementation of the Clinical Trials Directive 2001/20/EC (CTD) in 2004 resulted in compliance with the principles of GCP becoming a legal requirement for all those involved in the conduct of a clinical trial involving a medicinal product within the EU. This was further developed by the publication and implementation of the GCP Directive 2005/28/EC in 2005.
- 3.2. 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. It was proposed that further guidance would be published for non-commercial trials to indicate where certain aspects of GCP could be 'relaxed' for these trials specifically. However this has not been completed.
- 3.3. As a result, non-commercial trialists (and those who sponsor such research) believe that they must manage all aspects of trial conduct and GCP in a similar way to

commercial sponsors (such as the pharmaceutical industry). Many organisations now have concerns about not meeting all of the statutory requirements for the conduct of clinical trials. This has resulted in reluctance by some public sector organisations to participate in clinical trials, whilst others are adopting a risk-averse approach and requiring additional processes which have increased the cost and complexity of clinical trials.

3.4. A joint NIHR/MHRA/MRC-CTU project was established to help facilitate a risk-proportionate approach to applying the principles of GCP to the various types of clinical trial in the UK, within the context of the current regulatory framework in the EU, by:

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

4. Methodology

4.1. The pilot was designed to obtain comment and opinion from three different groups to ensure engagement with a variety of users and interested parties. The following groups were identified as being in a good position to provide useful, relevant feedback on the usefulness and appropriateness of the resource developed to date:

- Research Project Teams (funded HTA and EME programme clinical trials involving CTIMPS)
- Clinical Trials Units
- NHS Trust Research & Development offices

4.2. A list of potential participants was drafted by NETSCC and used as the basis for discussion with the MHRA.

4.3. Invitations to participate were issued in early March 2011 and participants informed that they would be required to provide feedback and comments by mid-April.

4.4. All participants were emailed a questionnaire produced by NETSCC and the MHRA (copy attached in Appendix B) and a draft version of the proposed guidance, which included monitoring plan templates, and asked to keep the documents confidential to those involved in preparing feedback. A contact at the MHRA was given in case of further questions about the guidance.

4.5. The questionnaire was designed to explore participant's opinions regarding the value and usefulness of the guidance resource and templates in undertaking their day-to-day trials-related activities and processes. Comments and feedback were also sought on any amendments and improvements that could be made to the documents and templates.

4.6. In addition the Project Teams were asked to complete a draft monitoring plan as per the guidance. A contact at the MHRA was supplied for assistance and advice in this process.

4.7. The number of participants returning completed questionnaires by the beginning of May (the deadline was extended to maximise participation) was:

- Research Project Teams – 6
- Clinical Trials Units – 5
- NHS Trust R&D Offices – 4

Draft monitoring plans were also completed by two of the Research Project Teams using the templates provided. In addition one other team supplied a monitoring plan in text format. These were forwarded to the MHRA for reference and comment.

The delays in providing feedback are largely attributable to the participants having insufficient capacity and other priorities. Specifically two draft monitoring plans were not provided due to one team having a high workload and feeling that it was difficult to do as a stand-alone exercise, and the other having no suitable staff in the office for a number of weeks over the consultation period (and colleagues were unable to assist due to potential conflicts of interest resulting from earlier involvement with the MHRA guidance).

4.8. Thematic analysis was undertaken on the completed responses. A process of progressive focusing occurred whereby topics were identified through an initial reading of the questionnaire responses. The topics were inevitably informed by the structure of the questionnaire. The topics were then clustered into a set of emerging themes after a re-reading of the responses. The range of responses relating to individual themes was then identified and is presented in section 5.

5. Results

SUMMARY FINDINGS

- Nearly all participants thought the risk-adapted and risk-proportionate guidelines and templates were valuable and timely.
- Feedback on the process of using the new approach was mixed with several participants finding the process straightforward whilst others finding it lengthy, complex and unclear.
- Specific criticisms of the process included the subjective nature of assessing Type B trials, the length of time caused by the need to involve many people in the application process, and the need for clarity on what happens if the MHRA disagrees with the investigator's / sponsor's risk assessment.
- Recommendations for modifying the approach typically focused on the need for greater clarity and improved structure.
- Participants had a mixed response when considering the impact of the approach on current practice. Several participants reported little change in the way trials are managed and monitored whilst others reported a beneficial or detrimental impact.

5.2.1 Value of risk-adapted approach

Most participants felt that a risk-adapted approach to managing and monitoring clinical trials would be valuable and useful. Principally this was because participants thought the approach would enable proportionate, appropriate and targeted assessments of risk. As one CTU respondent commented, '*We feel this approach is valuable as it will help us to look at trial risks in a proportionate manner with guidance given for three levels*' (CTU 1).

Several participants also welcomed the apparent reduction in bureaucracy and subsequent streamlining of monitoring and management processes. It was suggested this streamlining would result in a reduction to time and financial costs: '*The categorisation of IMP marketing status and standard medical care, aligned to three risk types, will definitely streamline the process of approvals and alleviate some*

of the costs/time implication in terms of monitoring when the trial is running' (Project 3).

Participants specifically highlighted the guidance on Type A and non-intervention trials being particularly helpful. Other advantages of the risk-adapted approach included: encouraging the use of existing information sources about the IMP, encouraging early engagement of sponsors in research by preparing risk assessments prior to application submission, and the adoption of a pragmatic and tiered approach to categorisation.

A few participants were critical of the risk-adapted approach. Two participants criticised the perceived subjective nature of the classifications: *'It relies on judgement by different groups/individuals (CI, Sponsor, Clinical Trials Unit, MHRA, Ethics) about the degree of risk and appropriate steps to mitigate the risks. But different people / organisations may come to different judgements at different times without any clear arrangement for determining which judgement takes precedence'*. (Trust R&D 1).

A few participants similarly thought the approach was vague. As one participant commented, *'there is a need to define what is meant by "monitoring" under non-intervention trials. Is telephoning a patient to find out how they are "monitoring"?'* (Project 6)

5.2.2 Suggested modifications to the risk-adapted approach

Many participants suggested the risk-adapted approach was unclear, vague and needed rephrasing. As one participant commented *'It is of no help to have guidance that is full of words such as "could", "should", "maybe", "probably"'* (Trust R&D 1).

Specific areas where clarity was sought were:

5.2.1.1 Off label use

A few participants felt the definition of 'off-label use' for Type A trials was too vague: *"Off Label Use" will need to be defined clearly as "sufficient published evidence and/or guidance" is open to interpretation'* (Project 3).

5.2.1.2 Trial Master File

As one participant commented: *'We felt that the guidance on a combined trial master file / investigator file on page 17 was unclear. Do you mean that a sponsor does not need to keep the Trial master file and the chief investigator can keep it?' (CTU 2)*. Similarly a Project award holder commented that practice delegation logs needed to be kept locally for reference and updating. Therefore, *'clear guidance must be given on this and on what should be kept in the TMF as opposed to the site file'* (Project 3). The participant went on to say that the combination of the TMF and ISF would not be practicable for multi-centre trials.

5.2.1.3 Reporting of Serious Adverse Events (SAEs)

Specific guidance was recommended on which Type B trials relates to the reporting of reductions of SAEs. One Project award holder felt the guidance on SAE reporting should be made clearer. They recommended specific templates for reporting of SAEs in Type A trials and a light touch approach to the regulation of trials with drugs being used within their licensed indications (P6).

Other suggested changes included:

- Flow charts – identifying times at which issues need to be addressed
- Explicit authorisation for Type A studies: *'The proposal that the MHRA only acknowledge receipt of a Type A application is bad governance and will lead to confusion'* (Trust R&D 1)
- Yellow card adverse event reporting for Type A trials
- Including an explanation of the different phases of trials I-IV
- A central surveillance office to be established rather than assessment via regional RD offices

- Combination of drugs as a potential risk modifier in Table 1 should be extended to include drugs combined with physical therapies
- A clear acknowledgement letter from the MHRA to act as the authorisation
- Clear training and guidelines for those carrying out risk assessments
- Inclusion of Japan and US licensed IMPs in Table 1
- The GCP compliance section on Page 9 over-encapsulation is classed as manufacturer – one CTU participant thought this was wrong and that the rules should not apply in this case (CTU 2).

5.2.3 The process of using the proposed risk-adapted guidance and templates

Participants presented a mixed response to comments on the process of using the risk-adapted guidance and templates. Several participants reported that the process was straightforward. One Trust participant commented that it was clear *'where risk adaptations are possible or not for each study type. A consistent approach to categorising studies into Types (based on the Adamon paper) will also introduce clarity across organisations and assist in decision making within the general risk assessment process'*. (Trust R&D 2) Other participants, however, found the process to be lengthy, complex and unclear. Particular problems were noted with terminology, which was seen by several participants as not being user-friendly for researchers. As a result, *'It would almost certainly need careful support from a CTU/Sponsor's office to complete'* (Project 4). It was suggested by that CTUs and administrators would be able to apply the new process more easily whilst others, such as non-commercial sponsors, would have greater difficulty: *'Although CIs and Clinical Trials Units are likely to complete the risk assessments they have an interest in underplaying the risks. Non-commercial sponsors (University and NHS Trusts) do not always have access to independent expertise to help assess the risks'*. (Trust R&D 1)

One Project award holder commented that the process of assessment was lengthy and complex due to the involvement of many individuals: *'The proposed process will require input of a clinical (phase of development / safety profile / implications) and possibly a pharmacist (interactions)...the more people that need to be involved, the longer the assessment would take.'* (Project 3)

It was suggested by one participant that the process for Type B trials was complicated due to the subjective nature of classifications: *'it's a question of how serious are the risks which are identified... What the QA manager considers to be a risk may well not be considered to be so by the CI'* (CTU 4).

Other areas of clarity included:

- No apparent place for sign-off of risk assessment, making it unclear who has responsibility
- No detail on what happens if the MHRA disagrees with the assessments.
- A lack of templates in appendix 1
- Nowhere to document fully how risk was assessed, even though risks to participant safety associated with the intervention are described on pages 19-20
- It is not clear what is required under the 'body system / hazard' heading.

5.2.4 Suggested modifications to the process for risk- adapted assessment

It was suggested that the risk-adapted process could be improved by adopting a clearer structure. One participant suggested a simplified overview *'highlighting the main areas of concern with better direction to the section concerned'* (Project 4). Greater clarity was also recommended for how amendments should be handled for Type A studies. As one participant commented, *'Is this document saying that they do not need to be notified to the MHRA?'* (Trust R&D 1).

Other recommendations relating to the design and delivery of the guidance and templates included:

- Re-organising appendix 1 into the three categories of Trials A, B and C.
- Including the Safety Monitoring Document as an Appendix to the Protocol rather than incorporated into the body of the protocol.
- A flow-chart / clear algorithms
- Filter questions on IRAS
- Worked examples of the risk assessment A, B and C templates.
- Cross-referencing sections in the trial protocol
- A simple web-based tool to support investigators
- A help-line

One further recommendation related to the delivery of the assessment process, involving a national R&D office for trials being set up in place of local R&D offices.

5.2.5 Comparison of risk-adapted approach to current practice

Participants presented a mixed response when comparing the new risk-adapted approach with current trials management and monitoring processes. Several participants reported that the new approach would not significantly change current practice as similar processes and categories were already being used. Other participants reported significant changes to trial management, particularly with category A trials. Other notable changes to current practice included greater clarity over classifications and undertaking risk assessments at an earlier stage.

The reduced role of the MHRA was viewed as a significant difference by one Trust participant, although they said that approval would still require the EudraCT application form to be submitted by the sponsor (Trust R&D 2). Another participant suggested that the new approach would make a difference to practice if CIs were deemed responsible and accountable by the MHRA for all aspects of a Type A study. (Trust R&D 1).

In terms of whether the new approach would result in improved or poorer processes, participants again presented differing views. One participant welcomed the new approach as they believed it would reduce administrative burden: *'The reduced administrative burden is welcome as is the agreement as to which documentation might not be required or can be merged'* (Project 1). Conversely, another participant suggested that the new approach would make risk adaptation more complicated as *'at present we risk assess by asking a series of very short questions without much explanation of why they are needed. But the questions are easier for researchers to understand.'* (Project 4).

One participant responded by detailing the fields they currently collect that would be missing in the new system. These included:

- Financial risk and IMP provision
- Capability and experience of the trial team
- Insurance / IP
- Facilities review.

5.2.6 Impact of risk adaptation process on business as usual

Participants had divergent views on the impact of new risk-adaptation processes on business as usual. Several respondents commented on improvements to their current activity, including a simplification of processes and a reduction in the amount of work involved: *'[the approach] would make a very significant difference to the trials we run, it would reduce the work involved and seem more appropriate.'* (CTU 2). It was suggested by certain participants that the benefits of the new process would be most notable for category A trials. One participant thought that the costs of conducting trials could be reduced as a result of the new approach (Trust R&D 3). In particular, costs could be reduced through changes in labelling and monitoring visit requirements for a limited number of trials (Project 3).

Other participants suggested that the new approach would generate problems. One participant suggested that the new approach would *'probably increase the workload of the Sponsor's office and increase timelines to approval'*. Another participant thought that the new process could result in *'an increase in paper work unless this was a replacement of the NIHR system and a directive to all NHS, Academic Institutes and Clinical Trials Units'* (Trust R&D 4).

One Project award holder through the new process would not impact on approval time: *'We do not think there will be any positive impact on the length of time to submission for regulatory approval, as the documentation required is not really reduced by post-approval.'* (Project 3)

Several participants made general comments on the impact of the new approach in terms implementing new forms, classifications, processes and SOPs.

5.2.7 General Comments about the risk adaptation process

Participants were invited to give general comments about the new process. Several participants took this opportunity to comment on the need for such guidance. Other participants however reiterated the need for an improved structure and clearer guidance. One participant commented on the subjective nature of risk assessment whilst another queried the role of MHRA, in particular whether MHRA fees would be different for assessing difference types of trials.

5.3 Part two: Guidance on Risk-Proportionate Approaches to the Management and Monitoring of Clinical Trials

5.3.1 Value of risk-proportionate approaches

Many participants felt the risk-proportionate approach to be valuable and helpful. Principally this was because the approach highlighted risks early (in advance of an application for funding), provided a risk-proportionate approach and generated greater consistency in risk assessment and therefore greater confidence in its application. As one participant commented, *'The risk-proportionate approach will be extremely useful when undertaking non-commercial sponsor related duties as it will assist in identifying risks within protocols, developing plans to mitigate these risks and developing appropriate trial monitoring plans. A consistent approach to this across the UK will also enable organisations to have confidence in externally sponsored non-commercial trials that they are hosting.'* (Trust R&D 2) Another participant commented on the importance of early engagement with risk assessment: *'Planning at the start of trial activity usually takes place but can sometimes be poorly documented. Use of the risk assessment template would be useful in formalising this in advance of an application for funding.'* (Trust R&D 3)

Conversely, one participant was critical of the new approach, suggesting that it was *'not much more than good practice guidance, which is useful regardless of whether a risk-proportionate approach is adopted by the MHRA.'* (Trust R&D 1). The participant when on to state that, *'there also appears to be considerable overlap with what the Ethics process is meant to assess and it is not clear how NRES is expected to respond to this.'*

5.3.2 Suggested modifications to the risk-proportionate approach

Participants made the following recommendations for improving the risk-proportionate approach:

- Stopping reporting for Type A trials and providing a summary at the end of the trial instead
- Specifying that electronic copies of primary source data are preferred
- A clear statement that risk can be perceived differently
- Not omitting issues listed in appendix 2 as not addressed

- Providing standardised documentation
- Providing exemplar protocols for Type A, B and C trials
- Including an assessment of associated costs to enable cross-referencing to the proposed costs associated with different trials
- Aligning tools in use with the RSS risk assessment tools where possible
- Changing the wording of the last column in appendix 2 to 'mitigation' rather than 'monitoring' to allow for a wider range of responses to be recorded.

5.3.3 The process of using the proposed risk-proportionate guidance and templates

Participants were divided in opinion over the process of risk-proportionate approach. Several participants found the guidance and templates clear and easy to follow: *'We wouldn't envisage any problems in completion of the process – the guidelines and information are easy to follow.'* (CTU1) Other participants, however, thought the approach to be 'wordy' and complex. One participant was concerned with the number of people required to sign off the risk-proportionate template and suggested that such engagement would result in no improvement in approval times. In addition, the participant expressed concern that *'a significant number of clinicians (especially those new to clinical trials) are not / may not be competent to assess risk in a regulatory / research context'* (Project 3).

One CTU participant thought that appending the safety monitoring template to the protocol would be a 'big hindrance' as they *'would not like to have to go back to ethics for protocol amendments'* (CTU 2). They also commented that *'it would not be feasible to complete the risk assessment at the pre-award funding stage (proposal development). We have limited resources to put together proposals and only a proportion of these go on to be funded'*.

One CTU participant (CTU 5) recommended particular areas of where clearer questions should be asked, including:

- Providing justification why a trial is not perceived to be a particular risk
- Answering yes or no to each section where each section asks several questions – the answer might not be the same for each question.
- Requesting information on patient withdrawal
- Considering the risk of fraudulent data and impact on data reliability
- Page 19 states that this does not address issues of training and experience of the trial team – where will these be addressed?

5.3.4 Suggested modifications to the process for risk-proportionate assessment

The following recommendations were made for modifying the risk-proportionate approach:

- Examples of completed templates
- A list of questions to ask, e.g. is the drug licensed?
- Having a section on SAE / Suspected Unexpected Serious Adverse Reactions (SUSARs) in the risk assessment tables at the end of the appendix
- Use of drop-down boxes
- Consideration of the extent to which the new process duplicates the RSS risk assessment
- Applicants should justify why answering 'no' for each area of risk.

5.3.5 Comparison of risk-proportionate approaches to current practice

Participants presented a mixed response when comparing the new risk-proportionate approach to their current trials management and monitoring processes. Several participants reported that the new approach would not significantly change current practice as similar processes and categories were already being used. One Trust

participant said they were already using a modified version of the RSS risk assessment tool and expressed a wish for the new approach to be aligned with this (Trust R&D 3).

Several participants commented that the most significant change to current practice would be the implementation of a more formalised, consistent risk assessment process conducted early on at the planning stage. Other changes were generally perceived to be beneficial, resulting in a less burdensome, proportionate centrally-based monitoring process: *'the proposals appear to allow for much less burdensome (and potentially more useful) centrally-based monitoring processes, adapted to the perceived risks of bias and poor data quality. This is welcome.'* (Project 2)

However, one CTU participant was concerned about any shift away from the use of site visits that could occur with a change in process: *'[site visits] are both important and necessary and we have written this into our SOP's as we believe this is best practice. If this is not made clear in this guidance document, then we think this will be a backward step.'* (CTU 4)

5.3.6 Impact of risk proportionate processes on business as usual

Participants expressed divergent views on the impact of new risk-proportionate processes on business as usual. Several participants reported little impact on business as usual as the new process reflected current practice. Other participants suggested the new process would yield benefits by simplifying processes for some trials: *'Overall we think our business would be simplified for some trials.'* (Project 2) Several participants commented that the implementation of new systems and processes was the chief impact, particularly completing the risk assessment before ethics application and submitting the RA/Monitoring plan with the CTA: *'We would do the risk assessment earlier, and would probably therefore have more detail included in funding proposals, which would be helpful.'* (Trust R&D 3)

Two participants expressed concern over the potential impact on work, time and resources: *'publicly funded trials...need ethics and regulatory approval before funding will be released. Hence these processes have to be covered by staff who are already in place and not covered by the trial grant. If this process has to happen as part of the Ethics / regulatory application and is going to include a monitoring plan – it is going to mean more work with no resource provided for it.'* (CTU 4)

5.3.7 General comments about the risk-proportionate process

Participants were invited to give general comments about the new process. One participant queried the difference between study type and study type plus when using the risk assessment to inform the monitoring plans (Trust R&D 4). Another participant took the opportunity to criticise the 'one size fits all approach' as *'there will be a lot of time spent trying to make the trial circumstances fit the form.'* (CTU 4)

One participant queried what would happen in the event of MHRA disagreeing with the assessment: *'If the MHRA were not satisfied with the content of the assessment and felt it was insufficient in detail, would they return the application? Would this then lead to any additional delays?'* (CTU 1).

5.4 General Comments

Participants were invited to provide general comments and observations about the proposed guidance and approaches. Several participants used this as an opportunity to comment on how much they welcomed the new approach. As one CTU participant commented, the guidance and templates *'Seems to be a very practical approach to the risks associated with trials, which should relieve some of the burdens we face in agreeing to undertake these trials at present as a non-commercial sponsor.'* (CTU 3) Another participant commented that, *'The proposed guidance and templates will assist all non-commercial organisations who routinely act as sponsors in CTIMPS, to ensure they are allocating the correct resource to studies and aid in unifying the processes across organisations. It will also help reduce the cost and*

complexity of certain trials, where systems and documentation are used that perhaps are not necessary, but have been implemented through concern of non-compliance with the regulations and the impact that negative inspection findings can have on institutions.' (Trust R&D 2) Other participants used this as an opportunity to reflect on the role of the MHRA. In particular, it was suggested that the MHRA needed to be *'much clearer in their guidance than they have been up to now'* (Trust R&D 1). One Project award holder thought that the MHRA should be more explicit in certain areas: *'For instance, mention should be made about factorial design or randomisation / re-randomisation design trials. Because these are not mentioned, the less knowledgeable think them suspect or even non-GCP.'* (Project 6) It was suggested by another participant that the GCP Inspection system leads to an overly risk averse culture: *'Further thought needs to be given to the GCP Inspection system. Generally this is regarded as quite positive by those organisations that have been inspected. But the process is geared to finding and reporting faults with systems rather than reporting on good practice and therefore, regardless of any intentions by the MHRA, the system does lead to many organisations becoming risk averse.'* (Trust R&D 1). One participant suggested the new approach should go further by restructuring R&D Offices: *'[R&D Offices] have become judge, jury and gamekeeper and are not subject to adequate control. Their role needs to be split. Local R&D offices should be concerned only with local resources, implementation and monitoring. There should be a national R&D office that decides on monitoring plans.'* (Project 6)

Other comments included:

- The Impact on international studies: The 'lighter touch' approach may not be appropriate for studies involving international co-investigators, collaborators, funders or sponsors due to their own requirements. (Project 3)
- The need for further guidance on how risk assessment should be used through the 'life cycle' of a trial.
- The appropriateness of undertaking RA prior to grants being contracted as this *'will strain already stretched resources'*. (CTU 4).
- The minimal impact of the new approach: *'The changes proposed for the low risk trials are either already in place or are so minimal as to make very little difference. Nothing in here will result in employing less staff, and that is where the costs lie.'* (CTU 4)
- The impact on NRES procedures: *'Currently NRES procedures for CTIMPs are different from non-CTIMPs. It is not clear how the sub-classification and stratification of CTIMPs will then affect the NRES procedures and if this will make things even more complicated.'* (Trust R&D 1)
- The impact on resourcing overheads by funders: *'Research funders generally do not take account of the administrative overheads of sponsoring clinical trials, particularly for NHS sponsors of academic studies. Unfortunately this guidance will probably give the funders further comfort that they don't need to invest in sponsor management and administration.'* (Trust R&D 1).
- The need to submit the protocol and IRAS form: *'Why do we have the clumsy split between the IRAS form and the protocol? For investigator led studies, should not IRAS and the protocol be one and the same document?'* (Project 6).
- The need to mention other study designs: *'Need to mention some of the less mainstream study designs just so that people know that you know that they exist and are not somehow "illegal", e.g. factorial, randomisation / re-randomisation.'* (Project 6).

6. Conclusions & Recommendations

- 6.1. This initial Pilot has produced several important observations that should inform the future refinement and development the MHRA 'risk-adapted approaches to the management of clinical trials of investigational medicinal products' resource.
- 6.2. Nearly all the participants (across all three groups) welcomed the activity and reported that the guidelines and templates addressed a current need, and were valuable and timely for the R&D communities.
- 6.3. Concern was expressed about the overall process, and some participants felt that length, complexity and clarity were an issue.
- 6.4. It would appear that there is a large variation in knowledge and awareness of the current regulations and requirements on the part of participants, especially Trust R&D offices. This may, in part, explain some of the differing interpretations of the draft guidelines and templates and reactions to them. There was also some reluctance to relax highly developed procedures, perhaps out of uncertainty about how these changes might be implemented
- 6.5. This Pilot would suggest that some further refinement is required, and that a focus on greater clarity and improved structure is required. It may be also that a high level of support from MHRA for units implementing these changes would be required until they have bedded in.

APPENDIX A

MRC/DH/MHRA Joint Project**Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products****Contents:**

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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
<p>Type A: no higher than that of standard medical care</p>	<p>Trials involving medicinal products licensed in any EU Member State if:</p> <ul style="list-style-type: none"> ▪ they relate to the licensed range of indications, dosage and form <p>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</p>
<p>Type B: somewhat higher than that of standard medical care</p>	<p>Trials involving medicinal products licensed in any EU Member State if:</p> <ul style="list-style-type: none"> ▪ such products are used for a new indication (different patient population/disease group) or ▪ substantial dosage modifications are made for the licensed indication or ▪ if they are used in combinations for which interactions are suspected <p>Trials involving medicinal products not licensed in any EU Member State if</p> <ul style="list-style-type: none"> ▪ the active substance is part of a medicinal product licensed in the EU <p>(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)*</p>
<p>Type C: markedly higher than that of standard medical care</p>	<p>Trials involving a medicinal product not licensed in any EU Member State</p> <p>(A grading other than TYPE C may be justified if there is extensive class data or pre-clinical and clinical evidence)*</p>

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

**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. These 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.

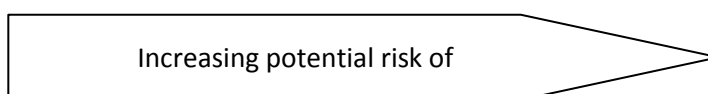
Active sponsor and trial team oversight during the course of the trial will be essential in any risk-adapted model. This will ensure that escalation/moderation of activity in response to incoming data and feedback on trial progress/conduct can occur, as appropriate.

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.



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)	(Yes)
5. IMP management	*	Yes	(Yes)	No
6. Documentation	*	Yes	(Yes)	(Yes)
7. GCP Inspections	*	Yes	(Yes)	No
	*	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 patients 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	<ul style="list-style-type: none"> a) IMP dossier b) Investigator's Brochure c) Good Manufacturing Practice (GMP) Compliance
3. Labelling of trial drugs	<ul style="list-style-type: none"> a) Need for trial labelling b) Content of labelling
4. Safety Surveillance	<ul style="list-style-type: none"> a) Adverse Drug Event recording/reporting b) Safety Monitoring

<p>5. IMP management</p>	<p>a) Tracking and Accountability</p> <p>b) Storage</p>
<p>6. Documentation</p>	<p>a) Trial Master File (TMF) Content</p> <p>b) Essential Documents retention times</p>
<p>7. GCP Inspections</p>	<p>a) Organisation and selection processes for routine GCP systems inspection</p> <p>b) Inclusion in routine GCP inspection reviews at the study level</p> <p>c) Frequency and duration of inspections</p>

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, a moderate- instead of a high-risk trial could be applied. 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 IMP dossier. 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 applies to 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 could apply to 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.

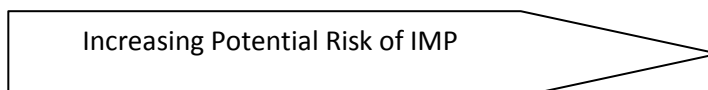
This could apply to Type A trials.

(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

Appropriate measures should be in place to provide assurance that the trial medication was taken by the participants in the trial, on the occasions proscribed by the protocol and in accordance with the trial design and randomisation procedures. The further away from standard practice the trial is, the greater the record-keeping requirements are; consequently for trials with products which have no authorisation (intended for Regulatory Submission) (Type C) and in some trials with designs markedly different from standard care (Type B), ICH GCP-style records of accountability would be expected (See ICH Document E6: Good Clinical Practice section 4.6.)

For Type C and some Type B trials documentary evidence of a full chain of custody from supply to destruction, from which both the quantities and quality of the trial product used can be determined, will be required.

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; furthermore 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:

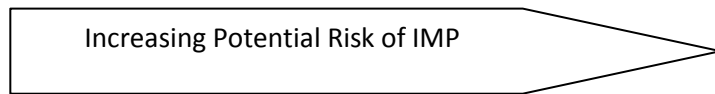
For trials designed to determine 'real use' of products, alternative measures such as trial participant diaries and questionnaires, coupled with the pharmacokinetic or other trial measures may provide valuable data in support of the trial, rather than detailed accountability logs, which may prove impractical 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).

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 intended use and influence of the trial results. For example there will be significant differences between trials which will be analysed on a per protocol basis compared to those analysed on an intention-to-treat basis in the need to record every dose for each participant.

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).

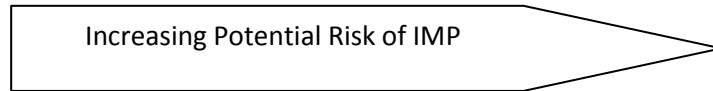
For Type C trials these must be included in the protocol to ensure all participating sites are aware of them. Furthermore, the extent of available stability data should support the extent of any proposed reporting of deviations/excursions from these requirements.

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, in general 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) Trail Master File (TMF) Content

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 can be open to interpretation, and, as a result, to date an accepted framework for this documentation has been described in ICH GCP E6 Section 8, particularly sections 8.2 to 8.4 and guidance on the TMF and Archiving in Volume 10 for Clinical Trials. It has therefore become a common basis for the Sponsor’s monitor, auditors and inspectors to review trial files against these standards, however, ALL documentation generated; including that produced by following a quality system; 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.

Application of risk adaption to trials impacts the Trial Master File documents as documentation normally present (for example, as defined in Volume 10 Guidance, ICH GCP E6) may be:

- **Replaced** by a document that serves a similar function, but does not carry the title presented in ICH GCP E6 Essential Documents*.
- **Combined** so that one document serves a number of purposes
- **Removed**, or not present as a result of implementation of the adaption measures

*Note: under the UK regulations (SI2004:1031 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 summarises the impact on the trial documentation from the adaptations 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

Increasing Potential Risk of IMP



Document	Type A	Type B	Type C
<i>Documents described in ICH Essential Documents</i>			
Investigators Brochure (IB)	Yes	(Yes)	No
IB Update†	No(N/A?)	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

APPENDIX A

Draft 4th March 2011

Additional documentary considerations resulting from the Directive:

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

Document	Type A	Type B	Type C
<i>Documents described in Directive 2001/20/EC &/or Directive 2005/28/EC</i>			
Investigational Medicinal Product Dossier	Yes	(Yes)	No
Manufacturer's Authorisation for Investigational Medicinal Product (MIA (IMP))	Yes	(Yes)	No
Manufacturer's Authorisation (MA)	No	No	No
Authorisation for IMP Importation	No	No	No
Qualified Person Certification (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	Adaption Possible
<i>Documents described in ICH Essential Documents</i>	
Safety Surveillance (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	Adaption Possible
<i>Documents described in Directive 2001/20/EC &/or Directive 2005/28/EC</i>	
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 regimen 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. However, for multi-centre trials, the establishment of files to oversee all investigator sites may result in the need for the file to span several volumes.

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 to:

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

The guidance and attached templates cover 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. ***They do not address issues associated with the training and experience of the trial team, host sites or other institutions involved in the conduct of a study.***

The templates are designed to be completed in advance of an application for funding for the study and in parallel with the development of a detailed protocol. The study design, risk mitigations*, safety monitoring procedures and trial management plans included in the protocol should 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.

The main objectives of this process are to:

- Provide a common language for, and structured approach to, risk assessment, trial management and monitoring planning - to facilitate discussions between stakeholders, including investigators, sponsors, funders, regulators 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 the Trial Intervention Safety Monitoring Plan).
- Assist investigators in planning the resources required for the appropriate management of the study.

* 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 and development of proportionate management plans

This is considered in two sections:

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

It is suggested that the attached safety monitoring template is completed and used, either as an appendix to the trial protocol or incorporated into the body of the protocol. It will be used during the assessment of the Clinical Trial Authorisation (CTA) application for the trial and agreed as acceptable (or not) by the MHRA assessors in the response notification.

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

Issues to be considered in the assessment

- 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 all 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?
- May concomitant medications increase the risk, i.e. interactions?
- What are the implications of the status of the product for patient safety monitoring e.g. vital signs; clinical examination; laboratory investigations; ECG; imaging; histopathology
- *Are any other risk mitigation strategies necessary, such as*
 - Restrictive eligibility criteria, e.g. exclusion of individuals at particular risk of harm 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); 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 reporting may be extensive (all AEs regardless of relatedness or seriousness) or may be more focussed (e.g. organ-specific, or serious AEs only), but 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 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; and an independent Data Monitoring Committee allows 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
 - the clinical procedures specified by the protocol;
 - failure to obtain fully informed consent;
 - failure to protect personal data; and
- 2) risks to the reliability of results

In the attached template, a similar process is outlined for all these areas of risk. A simple Yes/No classification is proposed to indicate whether or not there are any aspects of the protocol that materially increase the risks in areas outlined below. The specific hazards should be identified, and for each the appropriate mitigation, management and optimal monitoring should be considered.

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.

Issues to be considered in the assessment

- 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, 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 would probably be judged to be lower than if experimental treatments were being tested.

In 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. In this instance, the effect of the time constraints on participants should be considered in both the protocol and risk management plans.

Issues to be considered in the assessment

- 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 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).

Issues to be considered in the assessment

- Sensitivity of the data being collected
- Personal identifiers associated with the data
- Consent of the participant to use and access to the data
- Consent to share the data with third parties (if relevant)
- 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 eligibility criteria that do not require absolute precision for the trial results to be useful
- 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 assurance methods should focus on results rather than merely on data quality. 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 can allow differences in outcome to be assessed reliably. This can be done even if data collection is not complete, provided that data quality does not differ systematically by treatment group. Even so, it is appropriate that investigators 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.

Data collection and handling methods that can 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, well-validated and tested database with 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

For single-centre or small studies, the case report form and database may be simple.

However, they should have appropriate controls in place to assure the quality of the data captured and analysed, in-line with the criteria above.

Issues to be considered in the assessment:

(i) Robustness of the trial design

- Eligibility criteria:
 - Complexity
 - 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 (e.g. complex chemotherapeutic regimen with multiple drugs, different doses and dose-adjustments)
 - IMP management/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 unblinding during the course of the trial? Consider potential impacts of who has access to randomisation schedule, methods for emergency unblinding, whether unblinding of individual patients' treatment will be required before the end of the trial
- Outcome measures:
 - Degree of objectivity
 - Potential for standardised assessment
 - 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
 - Intensity
 - Complexity of procedures – extent to which they differ from normal care of the patient group
 - Impact and likelihood of non-adherence
- Power:
 - Is there sufficient power to comfortably detect the anticipated effect of the intervention

(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
- Methods of data transfer from primary data to database to final analysis file

Risk-adapted trial monitoring plans

Trial monitoring is not a standardized activity that should be implemented in an identical way in all trials. 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.

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, and that the 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 the risks.

The extent and nature of monitoring should be determined prior to the start of the 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. The risk assessment template accompanying 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.

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 now 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
 - Calendar checks
 - Checks for unusual data patterns
 - Assessment of adverse event and toxicity reporting rates
 - CRFs completed by authorised persons
 - External verification of events (e.g. birth, disease and death registries)
- On-site monitoring visits:
 - Ongoing 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

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 all the risk assessments above, and provides guidance for investigators and sponsors to determine the focus 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.

APPENDIX A

Draft 4th March 2011

		Concerns identified in the assessment of risk associated with the design and methods of the trial (other than the intervention)	
		No	Yes
Potential risk of the IMP/ intervention	Type A	<p>L</p> <p>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</p>	<p>L+</p> <p>As outlined in L, plus appropriate monitoring to address the specific vulnerabilities associated with the design and methods identified in the risk assessment.</p>
	Type B	<p>M</p> <p>Central monitoring of safety data quality and timeliness as well as protocol adherence and quality of other trial data.</p> <p>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).</p>	<p>M+</p> <p>As outlined in M, plus appropriate monitoring appropriate monitoring to address the specific vulnerabilities associated with the design and methods identified in the risk assessment.</p>
	Type C	<p>H</p> <p>More intense monitoring than above to have confidence in the completeness and reliability of safety data</p>	<p>H+</p> <p>As outlined in H, plus appropriate monitoring to address the specific vulnerabilities associated with the design and methods identified in the risk assessment.</p>

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.

Where central monitoring methods predominate, 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).

Attachments

Attachment 1. Template for Patient Safety Monitoring Planning

It is recommended that when completed this table is either included in the protocol or is an appendix to it; for trials of investigational medicinal products it may submitted to the MHRA with the CTA application

Study Title:	
Risks associated with trial interventions <input type="checkbox"/> Type A ≡ Comparable to the risk of standard medical care <input type="checkbox"/> Type B ≡ Somewhat higher than the risk of standard medical care <input type="checkbox"/> Type C ≡ Markedly higher than the risk of standard medical care	Protocol ID:
	EudraCT No.:

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Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):*

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review,...)

DRAFT

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

Attachments

Attachment 2. Template for Risk Assessment and Trial Monitoring Planning

The purpose of this template is to assist in the assessment and documentation of the main risks that arise from the protocol and study procedures (other than those associated with the intervention). For each area of risk, a simple Yes/No classification is used to identify whether there are any aspects of the study that are of particular concern. For any aspect identified, the appropriate mitigation, management and monitoring strategy should be considered and documented.

Risk Category: Participant Safety and Rights	Particular risk? (Yes/No)	If yes, list specific concerns (see issues to be considered in the guidance)	If yes, how will risks be minimised?	If yes, could monitoring methods help to address concerns? (Specify)
Participant safety - clinical procedures e.g. Do clinical procedures differ from standard care, and if so, do they involve any additional risk to participants?				

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<p>Participant rights - vulnerability and consent e.g. Does the study population include any particularly vulnerable groups? Is there any reason that the participants in the trial would not be able to give truly informed consent?</p>				
<p>Participant rights - data protection e.g. Will personal identifiers be collected? Will particularly sensitive data be collected?</p>				

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Risk Category: Reliability of Results	Particular risk (Yes/No)	If yes, list specific concerns (see issues to be considered in the guidance)	If yes, how will risks be minimised?	If yes, could monitoring methods help to address concerns? (Specify)
Eligibility e.g. Does the trial require very precise assessment of eligibility for results to be applicable to the target population?				
Randomisation method e.g. Is there any possibility that the randomisation schedule would differ from that described in the protocol or that treatment allocation might be predicted prior to randomisation?				

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Intervention e.g. Is it a complex or technically difficult intervention/treatment regimen in which might be applied incorrectly?				
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Masking/blinding of intervention e.g. If it is required, is there any risk that it could be ineffective?				
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Guidance for Risk-Proportionate Approaches to the Management and Monitoring of Clinical Trials

Attachments

Endpoints e.g. Are any key outcomes subjective, or require complex assessment?				
Follow-up Is the follow-up schedule difficult? (e.g. longer/ more intensive than standard care)				

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<p>Power e.g. Is there concern that the study may have insufficient power to detect the anticipated effect of the intervention? Is the anticipated effect size plausible?</p>				
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Guidance for Risk-Proportionate Approaches to the Management and Monitoring of Clinical Trials

Attachments

<p>Data collection e.g. Are there complex data or incompletely tested CRFs, data collection or transfer methods?</p>				
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DRAFT

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

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

Peter Johnson	Chief Clinician
Kate Law	Director of Clinical Research

Department of Health

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)

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

Medicines and Healthcare Products Regulatory Agency (MHRA)

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 Policy 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, MCRN Clinical Trials Unit, Liverpool
Heather House, Oxford University & John Radcliffe Hospital
Martin Landray, Clinical Trial Service Unit, Oxford
Louise Mawer, MHRA GCP Inspectorate
Wilma van Riel, Birmingham Clinical Trials Unit

APPENDIX B

NETSCC MHRA Pilot:

**Guidance for Risk-Proportionate Approaches to the Management and Monitoring
of Clinical Trials**

EVALUATION FEEDBACK FORM

Participant details	
Name	
Location	
Trial(s)	

Please note the information above is for NETSCC use only and will not be forwarded elsewhere, nor will comments below be ascribed to any identified individual.

The text boxes will expand as needed.

Approach to Managing and Monitoring Clinical Trials

- 1a) Please explain how valuable you feel that this risk-proportionate approach will be, and whether you think it would be useful in your trials activity.

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- 1b) Please comment on any changes that you believe would make the approach more valuable and useful.

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Process

- 2a) Please comment on the ease of completing the process using the proposed guidance and templates.

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- 2b) Please suggest any modifications to the process which would make it easier to work through.

Comparison to Current Practices

- 3a) How does the proposed method differ to your current trials management and monitoring processes?

- 3b) How would your 'business as usual' be affected if the MHRA adopted the approach as currently described?

Further Comments

- 4) Please add any further comments or observations you would like to make.

Thank you for participating in this pilot and providing your feedback.

The information given on this form will only be used to inform NETSCC's response to, and the development of, the MHRA's proposed guidance for risk-proportionate approaches to the management and monitoring of clinical trials.

Please return your completed forms by **Friday 8 April 2011**.