

**How to prepare for an inspection for Good Clinical Practice by the Medicines and Healthcare products Regulatory Agency (MHRA): a guide for NHS organisations that sponsor or host clinical trials of medicinal products**

An updated guide incorporating the Medicines for Human Use (Clinical Trials) Amendment Regulations (the Amendment Regulations) 2006 which transpose the EU Directive (2005/28/EC) on Good Clinical Practice.

intentional blank page

## Executive Summary

This guidance is primarily for NHS organisations, to help them prepare for statutory inspection by the Medicines and Healthcare products Regulatory Agency (MHRA) in relation to the conduct of Clinical Trials of Medicinal Products. This guidance updates the previous document dated 31 Oct 2006 and incorporates feedback from a sample of NHS Trusts who have been inspected during 2006/7. Also the MHRA has published guidance to give assistance to sponsors formulating the response to their MHRA inspection report to ensure that this post-inspection activity is handled as efficiently as possible.

The update does not significantly affect the guidance and is presented, for your convenience, at Appendix I.

This document provides guidance on:

- The obligations on an NHS Trust when hosting or sponsoring CTIMPs;
- What an MHRA inspection is;
- How to prepare for an MHRA inspection;
- What it is like to be inspected by the MHRA; and
- Common findings from inspections conducted by the MHRA.

The appendices provide:

- A list of key definitions;
- A series of directed weblinks where readers can access further information;
- Assistance in deciding if a project is a CTIMP;
- Checklists of documents required for the conduct of a CTIMP;
- Example MHRA notification letter to an NHS organisation;
- Example internal letters to researchers;
- Examples of MHRA inspection plans; and
- Information on who helped prepare this report;

The recommendations are summarised overleaf.

**Recommendation 1: Consider reporting an MHRA Inspection as a risk**

Consider reporting the possibility of an inspection by the MHRA through local risk management procedures.

**Recommendation 2: Update your R&D database**

Identify all CTIMPs on your research database.

**Recommendation 3: Review clinical trial documentation**

For all CTIMPs ensure that there is an appropriate Trial File and that it contains sufficient documentation to reconstruct the conduct of the trial. The sponsor maintains a Trial Master File and the investigator maintains an Investigator Site/Project File.

**Recommendation 4: System development**

Consider the need for system development.

**Recommendation 5: Prepare a plan for communication with MHRA**

- Appoint only one contact for the MHRA to ensure coherent communication with the MHRA.
- Where possible include at least one member in the team with previous experience of, or training in, managing inspections.
- Where deadlines are tight the project lead should discuss revised deadlines with the Lead Inspector.

**Recommendation 6: Prepare a plan for communication with Investigator Sites and internal departments**

- Devise a communication strategy and communication plan, to include all Investigator Sites and internal departments.
- Ensure all communication with MHRA is via a project lead.
- Retain all letter and email communications, and document (and date) significant conversations.
- Retain all paper records in a secure location.
- Use strict version control for all documents required to arrange the inspection.
- Store electronic documents in a password protected area on the network immediately accessible to the project team to allow fast communication.
- Identify list of departments potentially involved.
- Remind researchers that this is a statutory inspection and if the MHRA wanted to meet with them, they need to be available.

**Recommendation 7: Prepare staff**

- Ensure that staff are knowledgeable about all relevant policies and procedures, and that training records are up to date.

**Recommendation 8: Plan remedial action**

- Produce an 'Areas of Work' or similar document to identify issues and plan any remedial action.

**Recommendation 9: Tips for the actual inspection**

- It is not always possible to keep to the exact timings of the plan so staff need to be made aware that the timings are flexible.
- A member of the organisation's project team should accompany the inspectors at all times.
- All interviews should be minuted by a member of the project team.

**Recommendation 10: Review your system against the common findings from inspections conducted by the MHRA**

- Test your systems for compliance.
- Document and prepare an action plan for any system development.

**Recommendation 11: Response to your feedback from the MHRA**

- When you respond to the inspection report read the MHRA guidance on how a sponsor should ensure that the post-inspection activity is handled as efficiently as possible.

## Contents

<b>Contents .....</b>	<b>5</b>
<b>1 Introduction .....</b>	<b>7</b>
1.1 Types of GCP Inspection .....	7
1.2 Scope and Purpose of this Guide .....	7
1.3 Comments .....	8
<b>2 What are the obligations on an NHS organisation when hosting or sponsoring CTIMPs? ...</b>	<b>9</b>
2.1 Good Clinical Practice in non-commercial trials.....	9
2.2 The requirements on NHS organisations acting as sponsor.....	9
2.3 The requirements on NHS organisations acting as host.....	10
<b>3 MHRA GCP inspection in non-commercial organisations .....</b>	<b>11</b>
3.1 Sponsor inspection.....	11
3.2 Investigator site inspection.....	11
3.3 Pre-inspection activities for routine inspections .....	11
3.4 Activities of interest .....	11
3.5 The inspection .....	12
3.6 What will the MHRA be looking at?.....	12
3.7 Types of findings .....	12
3.8 Post-inspection MHRA report to the organisation.....	13
<b>4 How to prepare for an MHRA inspection.....</b>	<b>14</b>
4.1 Organisational culture .....	14
4.2 Project review.....	14
4.2.1 Identify projects that are CTIMPs .....	14
4.2.2 How to recognise a CTIMP.....	15
4.2.3 Allocation and delegation of responsibility.....	15
4.2.4 Check the trial files for each trial.....	15
4.3 System development.....	16
<b>5 What is it like to be inspected by the MHRA? .....</b>	<b>17</b>
5.1 Introduction.....	17
5.2 Stage 1: Notification .....	17
5.3 Stage 2: Preparation .....	17
5.3.1 Develop a communication plan.....	18
5.3.2 Completing the dossier .....	18
5.3.3 Inspection plan.....	19
5.3.4 Preparing staff.....	19
5.3.5 Review CTIMPs .....	20
5.4 Stage 3: Inspection visit .....	20
5.5 Stage 4: Post-inspection .....	20
5.6 Some suggested Dos and Don'ts.....	21
5.7 General comments .....	21
5.8 Where to get help and advice .....	22
<b>6 Common findings from inspections conducted by the MHRA .....</b>	<b>23</b>
6.1 MHRA experience of non-commercial organisations.....	23
6.2 NHS organisation-wide .....	23
6.3 Contract management.....	23
6.4 Quality systems .....	23
6.5 Investigational Medicinal Product.....	23
6.6 Ethical approval.....	23
6.7 Informed consent.....	23
6.8 Pharmacovigilance .....	24
6.9 Research staff .....	24

6.10	Records retention and management.....	24
6.11	Information Management & Technology .....	24
6.12	Data Integrity .....	24
6.13	Miscellaneous findings .....	24
<b>7</b>	<b>Appendix A: Key definitions .....</b>	<b>26</b>
<b>8</b>	<b>Appendix B: Useful webpages .....</b>	<b>28</b>
<b>9</b>	<b>Appendix C: EU Commission algorithm defining clinical trials within the scope of the Clinical Trials Directive .....</b>	<b>30</b>
<b>10</b>	<b>Appendix D: Checklist of essential documents for CTIMPs .....</b>	<b>32</b>
<b>11</b>	<b>Appendix E: Example correspondence .....</b>	<b>35</b>
	Example letter: Advance notice of MHRA statutory GCP inspection .....	35
	Example letter: Advance notice to internal researchers conducting CTIMPs.....	39
	Example letter: Notice to investigators providing the timing of the MHRA Inspection .....	40
<b>12</b>	<b>Appendix F: Examples of MHRA inspection plans.....</b>	<b>41</b>
	Example 1 .....	41
	Example 2 .....	45
<b>13</b>	<b>Appendix G: Membership of the working group .....</b>	<b>47</b>
	Working Group .....	47
	Acknowledgements .....	47
<b>14</b>	<b>Appendix H: A Summary of Changes Impacting on Non-Commercial Sponsors and Investigators arising from the amendment to ‘The Medicines for Human Use (Clinical Trials) Regulations 2004’ .....</b>	<b>48</b>
14.1	Introduction.....	48
14.2	Sponsor’s Delegation of Functions .....	48
14.3	Content and Presentation of the Investigator’s Brochure .....	48
14.4	Retention of Documents and Archiving.....	48
14.5	Wording of the Conditions and Principles of Good Clinical Practice .....	49
14.6	Serious Breach of GCP or Protocol .....	50
14.7	MHRA Power to Inspect Studies Not Holding a CTA.....	50
<b>15</b>	<b>Appendix I: MHRA Inspection Findings: One Year On. Summary of Common Threads and Feedback from Recently Inspected Non-Commercial Sponsor Organisations .....</b>	<b>51</b>

## 1 Introduction

The EU Clinical Trials Directive (2001/20/EC) came into force on 1 May 2004 and has been transposed into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (the Amendment Regulations) were laid in Parliament on 20 July 2006 and came into force on 29 August 2006. The Amendment Regulations implement the EU Directive (2005/28/EC) on Good Clinical Practice and also include additional provisions relating to arrangements for payment of fees; notifying the licensing authority of serious breaches of GCP and/or the protocol; and the extension of the infringement notices (warning notices) regime<sup>1</sup>. Together the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 will be referred to as the Clinical Trials Regulations in this document.

This Clinical Trials Regulations regulate the conduct of Clinical Trials of Investigational Medicinal Products (CTIMPs). As a result, NHS organisations sponsoring and hosting CTIMPs must ensure that systems are in place so that CTIMPs can be managed and conducted in accordance with both the Research Governance Framework (2005) and the Clinical Trials Regulations.

The European Commission is currently consulting on the specific modalities that may be adopted for non-commercial research. Once finalised, these should be taken into account by NHS organisations sponsoring or hosting CTIMPs.

It is important to note that the amendment gives the MHRA powers to inspect trials not holding a CTA (when they should have them) to establish that they are clinical trials and to require suspension of such trials until all necessary approvals are obtained. The amendment provides for the MHRA to issue infringement notices in such circumstances.

### 1.1 Types of GCP Inspection

Two types of GCP inspection are currently undertaken: the routine inspection and the triggered inspection. Triggered inspections generally take place in response to regulatory applications and/or referrals where issues relating to data credibility and/or patient safety are investigated to answer specific questions. Triggered inspections may be study-specific or system-based. The process and procedures followed during a triggered inspection are usually communicated on a case-by-case basis by the lead GCP inspector. This guide therefore, will focus on the statutory routine inspection. Such an inspection will focus on the organisation acting as Research Sponsor but it may also include other organisations acting as recruitment sites.

Note: GCP inspection procedures will be subject to change from time-to-time especially in the light of new guidance from the European Commission and system development/improvement. In addition, the recent MHRA survey examining the activities of non-commercial organisations will enable the GCP Inspectorate to further develop non-commercial inspection models. It is important to note, therefore, that the MHRA will conduct inspections according to their current SOPs. The experiences outlined in this document are given as indication of what may happen during an inspection and not a definitive description of what will happen.

Information from MHRA on GCP inspections is provided on the MHRA website, [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodId=136](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodId=136), accessed 31 October 2006.

### 1.2 Scope and Purpose of this Guide

The purpose of this guide is two fold:

- To give a brief overview of the main areas an organisation may wish to review to ensure that research is conducted to the quality standards that the MHRA would expect; and
- To provide an account of the practical experience of being inspected by the MHRA.

---

<sup>1</sup> A summary of changes impacting on non-commercial Sponsors and investigators arising from the amendment to 'The Medicines for Human Use (Clinical Trials) Regulations 2004' can be found in Appendix H.

Key definitions are given in Appendix A. Details of the individual systems and how they can be implemented are outside the scope of this document. However, many NHS and other non-commercial organisations have well-developed websites and Standard Operating Procedures (SOPs) that offer an additional level of detail. Example documents from a number of organisations have been referred to in the document and a selection of websites has been listed in Appendix B. The inclusion or omission of any examples from this list does not reflect any aspect of quality.

This guidance was prepared by an *ad hoc* group of the NHS R&D Forum Research Governance Working Group. The group included individuals from organisations that had been inspected by the MHRA. A list of all individuals involved in preparing and reviewing this document is provided at Appendix G.

### **1.3 Comments**

This document will be updated periodically and if you would like to send comments these should be addressed to:

Janet Messer  
NHS R&D Forum  
Tel: 01570 421172  
Email: [janet.messer@rdforum.vispa.com](mailto:janet.messer@rdforum.vispa.com)

## 2 What are the obligations on an NHS organisation when hosting or sponsoring CTIMPs?

This section describes the background to some of the responsibilities of NHS organisations sponsoring or hosting CTIMPs.

### 2.1 Good Clinical Practice in non-commercial trials

GCP is a set of ethical and scientific quality standards for the design, conduct, recording and reporting of clinical trials that involve the participation of human subjects. Their purpose is to ensure that the rights, safety and well-being of trial subjects are protected, and that the results from clinical trials are credible.

#### Conditions and Principles of Good Clinical Practice for CTIMPs<sup>2</sup>

The UK Clinical Trials Regulations specify the following conditions and principles. It is worth noting that the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 changed the wording of some of the principles and brought about the addition of two new principles - 7 and 8.

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.
7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.
10. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
11. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.
12. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.
13. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998 are safeguarded.
14. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial.

### 2.2 The requirements on NHS organisations acting as sponsor

The UK Clinical Trials Regulations categorise the sponsor's responsibilities in three areas:

- Authorisations (e.g. CTA and ethics, amendments, end of trial)
- Conducting the trial to GCP
- Pharmacovigilance

Systems should be in place to allow an overview of the set up, conduct and close down of the trial. Due diligence should be exercised to ensure that these trials are run to the appropriate standards.

---

<sup>2</sup> From the updated Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

Monitoring activities (whether undertaken by the Trial Management Group or by the Trust) would need to be appropriate and proportionate to the risk of the trial.<sup>3</sup>

Note that the sponsor has overall accountability for the trial even if tasks (such as writing the protocol) have been delegated to the Chief Investigator (CI) or other individuals.

Further information on the allocation of sponsorship responsibilities can be found in the Clinical Trials Toolkit: [http://www.ct-toolkit.ac.uk/route\\_maps/stations.cfm?current\\_station\\_id=288&view\\_type=map](http://www.ct-toolkit.ac.uk/route_maps/stations.cfm?current_station_id=288&view_type=map), accessed 31 October 2006.

An example of how an organisation may wish to decide if it would like to act as Research Sponsor is provided at:

[http://www.ucl.ac.uk/biomed-r-d/forms\\_proced/project\\_spon\\_reg.doc](http://www.ucl.ac.uk/biomed-r-d/forms_proced/project_spon_reg.doc), accessed 31 October 2006

An example of how NHS organisations can provide guidance to researchers wishing to conduct CTIMPs under the Sponsorship of an NHS organisation can be found at:

<http://www.ich.ucl.ac.uk/ich/r&d/ctag.htm>, accessed 31 October 2006

### **2.3 The requirements on NHS organisations acting as host**

The NHS organisation is required to have procedures in place for conducting the trial in accordance with Good Clinical Practice and the Clinical Trials Regulations, including:

- Adequate training for all site staff and adequate training records;
- Ensuring clarity of roles and responsibilities (e.g. contracts and agreement, delegation log)
- Appropriate knowledge of the trial and quality systems in all peripheral departments (e.g. laboratories, radiology, medical records);
- Ensure systems and facilities are fit for purpose (e.g. computer systems, equipment)
- Conducting the trial in accordance with the protocol, including: informed consent; reporting of adverse events / reactions as per protocol (and urgent safety measures); unblinding procedures; and IMP accountability at the trial site; and
- Adequate trial documentation and archiving of trial documentation.

Note that the Sponsor of the clinical trial may fulfil some or all of these requirements, but NHS organisations should ensure that research conducted within their organisation meets the necessary standards as part of their research governance systems.

---

<sup>3</sup> For information on risk assessment and monitoring and management activities please refer to the MRC/DH Clinical Trials Toolkit ( [http://www.ct-toolkit.ac.uk/route\\_maps/stations.cfm?current\\_station\\_id=290&view\\_type=map](http://www.ct-toolkit.ac.uk/route_maps/stations.cfm?current_station_id=290&view_type=map), accessed 31 October 2006)

### **3 MHRA GCP inspection in non-commercial organisations**

One of the requirements of the EU Clinical Trials Directive is that Member States set up inspection systems to ensure compliance with the Clinical Trials Regulations, and so the MHRA has established a GCP Inspectorate to conduct GCP inspections; one of a range of inspections that are carried out by the MHRA<sup>4</sup>.

The UK legislation defines the responsibilities of the Sponsor and the Investigator site. NHS organisations conducting clinical trials may be subject to inspection of either of these responsibilities.

#### **3.1 Sponsor inspection**

Where the organisation is named as the sponsor or co/joint sponsor of the CTIMP, the MHRA may conduct a 'sponsor' inspection. The sponsor has responsibility for the initiation, management and financing (or arranging the financing) of the trial. The sponsor is required to satisfy the MHRA that the study meets the relevant standards and to ensure that arrangements are put and kept in place for management, monitoring and reporting. An MHRA inspection will include scrutiny of trust-wide systems to confirm that the organisation has fulfilled its sponsor responsibilities.

#### **3.2 Investigator site inspection**

Where the organisation is hosting an investigational site, (with an external sponsor) the MHRA may conduct an 'investigator site' inspection. This is an inspection of the conduct of the trial by the investigator and of the role of the sponsor in overseeing the trial. Any NHS organisation systems that are used to conduct the trial will be scrutinised to ensure that they are "fit for purpose".

#### **3.3 Pre-inspection activities for routine inspections**

The MHRA will issue a letter of notification 2-3 months in advance. The organisation is expected to produce, within 28 days, a 'Pre-inspection Dossier' that will contain:

- Organisation details
- Contact name to manage logistics
- Details of clinical trials of medicinal products
- Index of Standard Operating Procedures and processes

The inspector will then review the dossier and agree inspection dates and the agenda with the organisation. Additional updated details may be requested nearer the date of the inspection.

#### **3.4 Activities of interest**

The MHRA will be interested in processes relating to:

- Regulatory submissions
- Laboratories
- Investigational medicinal product management
- Contract Management
- Project management
- Trial-file management for selected clinical trial(s)
- Quality Assurance
- Training
- Computer systems
- Monitoring
- Pharmacovigilance
- Medical Advisors
- Data management
- Statistical Analysis

---

<sup>4</sup> Other types of inspection carried out by the MHRA include Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Phase I Units

- Report writing
- Archives
- Investigational sites

### 3.5 The inspection

There will be an opening meeting to confirm the purpose of inspection, provide introductions and methodology. The inspection will be conducted generally in accordance with a predetermined plan, though this may be revised based upon inspection outcomes. The inspection will include a combination of staff interviews, document review and facility visits. The MHRA are likely to use study-specific examples to demonstrate the system. The MHRA will provide feedback of general findings at a closing meeting.

The inspection will be characterised by:

- Flexibility on both sides
- Open dialogue from the beginning
- Ongoing verbal feedback throughout the inspection
- Opportunity to demonstrate how your systems meet the legislation
- Review of action plans already in place to address known areas of non-compliance

### 3.6 What will the MHRA be looking at?

The Inspection may examine the following

- Is the trial being conducted in accordance with the principles of GCP?
- Is there a controlled process for writing, review and approval of protocol amendments?
- Is there an adequate pharmacovigilance system in place?
- Have the appropriate authorities been notified? (including early termination)
- Interaction with ethics system, regulatory authority, or collaborator / sponsor

### 3.7 Types of findings

The inspection report will specify the criteria used to categorise findings. However, in previous inspections, the MHRA have used the following criteria:

- Critical;
- Major; or
- Other.

A 'Critical' finding was defined as one where:

- Evidence exists that the safety, well being or confidentiality of trial subjects has been (or has significant potential to be) jeopardised, and/or,
- Serious doubt exists relating to the accuracy or credibility of trial data.

A 'Major' finding was a non-Critical finding that:

- Reveals a significant and unjustified departure from the UK regulations or,
- Consists of a number of minor departures from the UK regulations or other relevant established guidance, suggesting a systematic quality assurance failure, and/or,
- Reveals a failure to comply with relevant legislative requirements.

An 'Other' finding was any other inspection finding, including observations and recommendations.

The implications are:

- Critical findings require an agreed remediation plan to be put in place and re-inspection can occur.
- Major findings must be addressed but the organisation suggests to the MHRA how this is achieved.
- Other findings do require remedy where this is possible, and preventative actions should always be considered. Response to other findings will be requested in the inspection report.

Observations and recommendations do not require written response unless requested by the Inspector in the inspection report.

### **3.8 Post-inspection MHRA report to the organisation**

A report is issued within 30 working days of the end of inspection. The MHRA will expect responses to be received within 30 calendar days of despatch. There will be an opportunity for questions and clarification, if required. The MHRA will issue a summary letter and an inspection certificate.

## 4 How to prepare for an MHRA inspection

In practice, the task of ensuring that systems and processes for managing and conducting CTIMPs are “fit for purpose” will probably fall on the R&D Manager or R&D office. These systems and processes should be in place whether or not an inspection is due to take place. The activities described in this section should take place in all organisations sponsoring or hosting CTIMPs. Do not wait to be notified of an inspection before preparing for inspection.

There are three broad groupings of activities that you should consider:

- Organisational culture
- Project review
- System development

### 4.1 Organisational culture

Perhaps the most difficult task facing the R&D Manager is to change the culture of the organisation. How do you get clinicians, nurses and managers to recognise the seriousness of an MHRA inspection before it actually takes place? How do you hold them to account when you are probably not in a position of seniority?

It is not possible to predict the likelihood of an inspection due to the range of criteria used by the MHRA in selecting inspection sites. If an organisation sponsors or hosts CTIMPs and systems and processes for managing and conducting CTIMPs are not in place or inadequate, the consequence for the organisation may be substantial.

The following list suggests some methods you may use to help cultural change:

- Involve the risk management processes already in place in the organisation.
- Create a steering group to manage the change process.
- Get the Chief Executive and/or Medical Director to write to all researchers involved in clinical trials explaining the importance of the change.
- Circulate documents describing the experience of other organisations that have had MHRA inspections.
- Organise an awareness event, perhaps with outside speakers to ensure researchers understand why these changes have to be implemented.
- Set aside administrative resources to assist with paperwork.

#### **Recommendation 1: Consider Reporting an MHRA Inspection as a Risk**

Consider reporting the possibility of an inspection by the MHRA through local risk management procedures.

### 4.2 Project review

#### 4.2.1 Identify projects that are CTIMPs

The first thing the MHRA will do on inspection is ask for a list of the IMP trials you are hosting and sponsoring so that they can plan the inspection. At the very least this list should be complete, accurate and easily available.

NHS organisations often have a database or spreadsheet to store information on their research activity. It is recommended that all CTIMPs are easily identifiable. While you do this you may like to note the following points:

- Double-check older trials to make sure they do or do not come under the Clinical Trials Regulations. It is worth reading the titles and methodologies of older trials to make sure you do not miss any.
- Write to all researchers asking them to check whether their research meets the definition of a CTIMP.

- Do not assume that finished trials will not be inspected, particularly multi-centre trials that may still be running elsewhere.
- Make sure you identify and check who the sponsor is.

#### **Recommendation 2**

Identify all CTIMPs on your research database.

#### **4.2.2 How to recognise a CTIMP**

The European Commission has published an algorithm to help you decide whether your clinical trial is a CTIMP. This algorithm can be accessed at:

[http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04\\_2006/clinical\\_trial\\_qa\\_april\\_2006.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04_2006/clinical_trial_qa_april_2006.pdf), accessed 31 October 2006. If there is doubt over the trial in relation to whether it is a CTIMP guidance may be sought from the MHRA Clinical Trials Unit. It is recommended that records of this correspondence are retained.

#### **4.2.3 Allocation and delegation of responsibility**

The NHS organisation needs to be clear which activities it is going to perform through its R&D team and which activities are going to be delegated to the Chief Investigator. It is worth noting that if the NHS organisation is the sponsor, the task can be delegated but the sponsor remains accountable, so systems to ensure that any delegated responsibilities are being performed appropriately should be considered.

For example, many organisations delegate safety reporting (the production of annual safety reports and expedited reporting of SUSARs) to the Chief Investigator. However, as these are complex requirements, some NHS organisation have decided to facilitate this by providing Chief Investigators with example templates for the annual safety report and also being involved in the SUSAR reporting process to ensure statutory timeframes are met.

Standard Operating Procedures and agreements should clearly define responsibilities of the Chief Investigator and the NHS organisation.

#### **4.2.4 Check the trial files for each trial**

All Principal Investigators for CTIMPs should have an Investigator Site File that contains sufficient documentation to reconstruct the conduct of the trial at that site.

Sponsors should ensure that a Sponsor Trial Master File is maintained. If the organisation has delegated the responsibility for the maintenance of the Trial Master File to the Chief Investigator, check that you know where this information is kept for each sponsored CTIMP. Each file should contain sufficient documentation to reconstruct the conduct of the whole trial.

Many NHS organisations use modified versions of Section 8 of the ICH GCP guidelines as a basis for their file requirements. European Commission guidance including specific modalities for non-commercial research will clarify the minimum requirement for documentation. The draft document is available at

[http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/07\\_2006/guide\\_noncommercial\\_2006\\_07\\_27.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/07_2006/guide_noncommercial_2006_07_27.pdf), accessed 31 October 2006.

#### **Recommendation 3**

For all CTIMPs ensure that there is an appropriate Trial File and that it contains sufficient documentation to reconstruct the conduct of the trial. The sponsor maintains a Trial Master File and the investigator maintains an Investigator Site/Project File.

### 4.3 System development

Examples of the systems that should be in place to achieve compliance with the principles of GCP are given below:

- Contract Management
- Document Management
- Report Writing
- Project Management
- IMP Management
- Archives
- Monitoring
- Regulatory Submissions
- Laboratories
- Pharmacovigilance
- Quality Assurance
- Trial master file
- Data-management
- Training
- Report Writing
- Statistical Management
- Computer Systems
- Archives

Details of how to develop and implement these systems is outside the scope of this document. Major changes to systems and processes should not be undertaken immediately prior to an inspection, as it is unlikely that appropriate training and implementation could be achieved alongside the preparation and briefing required for the inspection. Section 6 provides information on reviewing existing systems and planning system development. Further details and examples of systems can be obtained via the websites listed in Appendix B.

**Recommendation 4**

Consider the need for system development.

## 5 What is it like to be inspected by the MHRA?

### 5.1 Introduction

From 1997 to May 2004 the MHRA operated a voluntary GCP inspection programme, developing methods to conduct statutory GCP inspections. The statutory programme for GCP inspections began in May 2004. The purpose of this section is to provide information based on the experience of five non-commercial organisations that have been inspected under both the voluntary and statutory programmes. The processes used by the MHRA in undertaking inspections may change over time, so this section cannot be used as a definitive guide to what will happen in any future inspections. Example documents provided in the appendices were current at the time of writing but may be subject to change.

The GCP inspection process experienced by organisations contributing to this document can typically be divided into four stages. These are notification, preparation, inspection visit and post-inspection.

### 5.2 Stage 1: Notification

Under the statutory programme, once selected by the MHRA for GCP inspection, the organisations received an 'Advance Notice of MHRA Statutory Inspection' (see Appendix E, Typical MHRA letter: Advance Notice of MHRA Statutory GCP Inspection). It is worth pointing out that the MHRA formally inform the organisation acting as Research Sponsor but do not notify other organisations which may be acting as an Investigator Site.

The Advance Notice typically included the following:

- Letter stating the purpose of inspection.
- Information on General Requirements
- List of items required pre-inspection
- MHRA GCP Statutory Inspection Programme Advice Note

The documents had to be provided to the MHRA within 28 days of the date of the request.

The MHRA will charge a fee for inspections in order to fund the activities of the GCP Inspectorate. A consultation document has been published proposing a revised fee structure from April 06. Details of clinical trial inspection fees can be found on the MHRA website, <http://www.mhra.gov.uk>, accessed 31 October 2006.

### 5.3 Stage 2: Preparation

Organisations identified an individual to act as 'Project Lead'. The MHRA identified the Lead Inspector. A dialogue between these two Leads continued up to the inspection. The Project Lead required assistance from one or more other members of staff dedicated to preparing and undergoing the inspection, the number of staff allocated depended on the size of the organisation. The Project Lead and team may be identified in accordance with prior agreed arrangements and Standard Operating Procedures.

#### **Recommendation 5**

Prepare a plan for communication with MHRA:

- Appoint only one contact for the MHRA to ensure coherent communication with the MHRA.
- Where possible include at least one member in the team with previous experience of, or training in, managing inspections.
- Where deadlines are tight the project lead should discuss revised deadlines with the Lead Inspector.

### 5.3.1 Develop a communication plan

Informing all staff at an early stage proved beneficial, as when staff were approached to provide documentation for the Dossier, they had been pre-warned, felt involved in the process, understood the importance and were, on the whole happy to provide the information within very tight deadlines. An example plan is given below.

- 1) The Director of Research and Development informed the Chief Executive.
- 2) Letters/emails were sent to:
  - Trust Executives
  - Clinical Directors
  - Research Leads
  - General Managers
  - Principal Investigators
  - Researchers
- 3) All recipients and in particular General Managers and Principal Investigators were asked to cascade the information down to all staff and researchers.
- 4) Principal Investigators included on the list of CTIMPs notified to the MHRA in the dossier were informed that they were on list and may be inspected.

Example letters are provided in Appendix E:

Example letter: Advance Notice to internal Researchers conducting CTIMPs

Example letter: Notice to Investigators providing the timing of the MHRA Inspection

#### **Recommendation 6**

Prepare a plan for communication **with Investigator Sites and internal departments**

- Devise a communication strategy and communication plan, to include all Investigator Sites and internal departments
- Ensure all communication with MHRA is via a project lead.
- Retain all letter and email communications, and document (and date) significant conversations.
- Retain all paper records in a secure location.
- Use strict version control for all documents required to arrange the inspection.
- Store electronic documents in a password protected area on the network immediately accessible to the project team to allow fast communication.
- Identify list of Investigator Sites and internal departments potentially involved.

Remind researchers that this is a statutory inspection and if the MHRA wanted to meet with them, they need to be available.

### 5.3.2 Completing the dossier

The 'Advance Notice' asked organisations to identify:

- Activities performed by the organisation on site in the conduct of clinical trials;
- Activities relevant to the organisation but performed at an alternative location (locations and relevant contact details required).

Activities at alternative locations refers to activities for which the organisation took responsibility and/or commissioned, thus, for example, central labs commissioned by an external sponsor company do not have to be listed.

The documents requested were obtained from the relevant departments and collated into one A4 lever arch file, as requested by the MHRA. Where possible, electronic copies of documents were also provided on a CD-ROM.

Having identified activities in which the MHRA were interested, it was possible to identify departments that could be involved in the inspection. These typically included:

Within organisation:

- R&D
- Pharmacy
- Information & Technology
- Radiology
- Laboratories
- Research and Development Support Unit
- Medical Records

Alternative Locations:

- Public health labs
- Database company
- ICH GCP trainers

Please note that if MHRA wish to access information relating to the REC, this will be done by direct contact between the MHRA and the relevant REC and not via the R&D office.

### **5.3.3 Inspection plan**

Following submission of the dossier, the project lead was contacted by the MHRA Lead Inspector to discuss and develop the inspection plan.

Typically, two or three studies were identified for inspection. Inspectors wished only to inspect non-commercially sponsored IMP clinical trials. Furthermore, during some inspections Inspectors were only interested in studies that were being sponsored by the organisation. Other criteria used to select studies included a high volume of patients recruited, complex design e.g. randomised double blind, and PIs performing a number of studies. Additional documentation was provided on request for the studies chosen for inspection, e.g. Patient Information Sheets, Consent Forms, Protocols and amendments and a list of randomised/recruited patients prior to the visit (initials and date of birth only).

The Inspectors identified by name, from the organograms provided in the dossier, the staff they wished to meet during the inspection. These departments typically included R&D, RDSU, local laboratories, Medical Records, Information Technology, and Pharmacy (including production and Quality Assurance). Staff identified were typically not the Head or Director of the Department but the 'person actually doing the job', e.g. Pharmacy Technician.

A draft inspection plan was received by email from the Lead Inspector. The project lead, or delegated person, contacted the relevant people to book appointments. Some negotiation was required. Some staff had to be reminded that the inspection was statutory.

Note: It is policy in some organisations that medical staff must give a minimum of 6-9 weeks notice to be relieved from clinical duties. The MHRA inspections typically allowed insufficient time to give such notice and some Medical Staff expressed a reluctance to cancel clinical duties. The issue was raised with the MHRA who advised that medical staff be reminded that the inspection was statutory and their presence was required. All medical staff made themselves available and there was no further debate. The issue of giving notice has been formally fed back to the MHRA.

The final inspection plan was agreed with the Lead Inspector, and meeting rooms were booked as required.

### **5.3.4 Preparing staff**

The final inspection plan was provided to all staff identified as being involved. These staff were briefed on what the inspector wished to see and why, and provided with up-to-date copies of relevant policies and procedures. It was important to alleviate as much anxiety as possible and re-assure staff that the inspections were positive events which would provide leverage to improve standards.

Where a single unit was inspected it was possible to provide in-house training to ensure all staff were up-to-date with regulations, policies and procedures.

**Recommendation 7: Prepare staff**

Ensure that staff are knowledgeable about all relevant policies and procedures, and that training records are up to date.

### 5.3.5 Review CTIMPs

All studies identified for inspection were subject to an internal review prior to the MHRA inspection. This included reviewing trial files against the checklist of essential documents (see Appendix D). Where possible, trial files were brought up to date.

Where organisations identified issues that fell short of required standards an 'Areas of work' or similar document was compiled to identify issues and indicate what remedial action was planned and when.

**Recommendation 8: Plan remedial action**

Produce an 'Areas of Work' or similar document to identify issues and plan any remedial action.

### 5.4 Stage 3: Inspection visit

The MHRA reviews organisational systems and policies and also inspects different studies to determine whether the organisation-wide systems and processes were actually being implemented and adhered to by site staff. Inspections were typically conducted by 2-3 inspectors over 3-4 days. Examples of full inspection plans are given in Appendix F.

The inspectors conducted interviews with staff, reviewed documents looking for evidence to back up information provided in interviews, and viewed facilities and computer systems. During interviews inspectors made additional requests for documentation. This could include documents or files relating to studies not previously identified for inspection. It was important to have a clear system for recording all requests, sourcing the documents (outside the interviews so as not to disturb), labelling the documents clearly (to allow the inspectors to match the document provided to the document requested) quickly and providing them promptly to the inspectors for review at times pre-allocated in the inspection plan. Where documents could not be located during the inspection these had to be sent on afterwards. All staff interviewed were asked if they had received GCP training and some staff were asked to produce evidence of such training.

**Recommendation 9: Tips for the actual inspection**

- It is not always possible to keep to the exact timings of the plan so staff need to be made aware that the timings are flexible.
- A member of the organisation's project team should accompany the inspectors at all times.
- All interviews should be minuted by a member of the project team.

### 5.5 Stage 4: Post-inspection

On receipt of inspection reports, organisations were given deadlines for responding to findings. Critical findings sometimes required a more rapid response (e.g. 14 days) with responses to major findings required within 28-30 days. The findings and response instructions were sent to the contact person in each department to which a particular finding related. Responses were collated by the project lead and returned to the lead inspector within the time allowed. Clarification on a few minor points were requested and sent. Following the provision of a satisfactory response the GCP Inspection Statement was issued to the organisation.

It is important to remember that responses must be implemented. Should an organisation be inspected again any Major findings that had not been addressed would automatically be escalated to Critical.

## 5.6 Some suggested Dos and Don'ts

---

Do	Don't
<ul style="list-style-type: none"><li>• Be completely open and honest at all times.</li><li>• Audit studies chosen for inspection prior to the inspection.</li><li>• Acknowledge and document areas that you know need development.</li><li>• Implement a thorough communication strategy.</li><li>• Provide information on relevant policies and procedures including GCP requirements to staff involved in the inspection in advance.</li></ul>	<ul style="list-style-type: none"><li>• Do not make Major changes to policies and procedures in the weeks leading up to the inspection.</li><li>• Do not write and implement Standard Operating Procedure that are overly complex and above the required standards. You will be inspected to your SOPs as well as the regulatory requirements. Failing to meet your SOPs will result in inspection finding even if you are meeting the regulatory requirements. Where possible use 'guidance' instead of rigid SOPs.</li></ul>

---

## 5.7 General comments

- Organisation-wide inspections highlighted that research is an integral function of all departments within the organisation.
- Inspections can assist in raising the profile of research within an organisation.
- Collating the documents and preparing the inspection plans required the R&D staff to work closely with previously unmet colleagues and assisted with developing excellent working relationships for the future.
- The inspection helped provide leverage to secure resources for and implement necessary changes to systems and policies.
- The vast majority of inspection findings related to failings in organisational systems rather than individual poor conduct.
- When developing any new system for research or addressing a research-related issue always consider how the situation would be viewed by an MHRA inspector and act accordingly.

## 5.8 Where to get help and advice

Contact name	Organisation	Contact email	Contact telephone	Contact address
Dr Jane Varey	Newcastle upon Tyne Hospitals NHS Trust	<a href="mailto:jane.varey@nuth.nhs.uk">jane.varey@nuth.nhs.uk</a>	0191 282 4823	Clinical Research Facility, Leazes Wing, RVI, Newcastle upon Tyne, NE1
Mr Ian Goodall	Oxford Radcliffe Hospitals NHS Trust	<a href="mailto:ian.goodall@orh.nhs.uk">ian.goodall@orh.nhs.uk</a>	01865 222757	R & D Department, Manor House, The John Radcliffe, Headley Way, Headington, Oxford OX3 9DZ
Sara Shankland	Velindre NHS Trust - Cancer Services Division	<a href="mailto:sara.shankland@velindre-tr.wales.nhs.uk">sara.shankland@velindre-tr.wales.nhs.uk</a>	029 2031 6222	Clinical Trials Unit Velindre Cancer Centre, Whitchurch, Cardiff, CF14 2TL
Christine McGrath	Southampton University Hospitals NHS Trust (inspection conducted when at United Bristol Healthcare NHS Trust)	<a href="mailto:christine.mcgrath@suht.swest.nhs.uk">christine.mcgrath@suht.swest.nhs.uk</a>	023 8079 4752	Trust Management Offices, Mailpoint 18 SUHT, Tremona Road, Southampton, SO16 6YD
Tomasz Kurdziel	University of Leeds/ Leeds Teaching Hospitals NHS Trust	<a href="mailto:t.j.kurdziel@leeds.ac.uk">t.j.kurdziel@leeds.ac.uk</a>	0113 392 6473	R&D, Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Leeds LS1 3EX

## **6 Common findings from inspections conducted by the MHRA**

This is based on a presentation given by the MHRA to the NHS R&D Forum Research Governance Working Group in Nov 2005 and from the experience of five non-commercial organisations that have been inspected.

### **6.1 MHRA experience of non-commercial organisations**

- Organisations are very open to recommendations & proactive in response to inspection findings
- Organisations are willing to develop systems through extensive networks
- Findings are often in-line with those identified by internal audit/R&D function
- Findings are very similar to those in commercial organisations

### **6.2 NHS organisation-wide**

- Potentially inadequate systems to ensure researchers do not commence research before all approvals are in place
- Unclear sponsorship arrangements for DDX studies rolled over to CTA studies
- Inadequate pharmacovigilance systems and/or inadequate use of systems in place
- Lack of written agreements between departments documenting role in IMP trials

### **6.3 Contract management**

- Omissions, errors and discrepancies in contracts
- Responsibilities of collaborating parties not clearly defined
- Unclear ownership of documents and data
- Lack of consistency between protocol and contract
- Many activities delegated to Chief Investigator without agreements or robust systems in place

### **6.4 Quality systems**

- Lack of essential SOPs
- Uncontrolled documents used in place of SOPs
- SOPs / Protocol do not reflect current practice or current legislation
- Insufficient time between issuing and implementing SOPs, leading to training issues
- Meetings and decisions not documented
- In-process checks not documented
- Internal audit programmes built around Research Governance Framework only and do not take account of Clinical Trials Regulations

### **6.5 Investigational Medicinal Product**

- Missing or unsigned documentation (e.g. shipping records, accountability, dosing records)
- Inadequate provisions for storage of IMPs i.e. not kept separate to usual clinical supplies
- Emergency codes not supplied concurrent with supplies or prior to study start
- Insufficient records for the chain of custody (from purchase to destruction) for marketed products used in clinical trials

### **6.6 Ethical approval**

- Lack of approval for study advertising
- Study conduct at sites outside of those in the application

### **6.7 Informed consent**

- No records of consent being taken

- Missing elements
- Inconsistencies with protocol
- Forms not updated with amendments, poor version control
- Incorrect form used
- Unclear process

#### **6.8 Pharmacovigilance**

- Lack of involvement of Principal or Chief Investigator
- Lack of awareness of legislative requirements (7 and 15 day reports)
- Failure to distinguish AEs and ADRs
- Failure to identify 'Serious events'
- Failure to consider event expectedness, and hence to identify events which require IMMEDIATE reporting
- Failure to monitor pregnancy to outcome
- Failure to monitor increased severity or frequency through trend analysis

#### **6.9 Research staff**

- Lack of evidence of GCP training amongst PIs and research staff
- Inadequate arrangements for cover in absence of PIs
- Poor document control and management
- Delegation logs incomplete. Delegated responsibilities not clear.
- Lack of documentary evidence of PIs involvement in trial e.g. informed consent procedure
- Unclear indemnity arrangements for honorary contract holders

#### **6.10 Records retention and management**

- Issues relating to record management outside the control of the Central Records Department.
- Facilities and offices used to temporarily store Medical Records of trial subjects, and trial-related documents, e.g. consent forms and CRFs, not sufficiently secure
- Tracing system may be inadequate for all records required to reconstruct clinical trial historically
- Inadequate retention period in radiology
- Inadequate retention of evidence of validation for alternative media used to store records
- Inadequate retention of QA and QC data in laboratories
- Inadequate retention of raw source data with implementation of electronic archiving

#### **6.11 Information Management & Technology**

- Lack of organisation-wide disaster recovery plan
- Lack of procedures and documentation to provide assurance that computer systems are demonstrably fit for purpose
- Some locally developed systems not sufficiently secure

#### **6.12 Data Integrity**

- Methods of analysis are inadequately documented (or have not been considered)
- Systems and procedures for data management (including assurance for the validity of the data) are absent, inadequate or failing

#### **6.13 Miscellaneous findings**

- Lack of documentation of validation of computer systems
- Lack of GCP training or evidence of training
- Study documentation not in secure place with restricted access
- Poor document control – involvement of Principal Investigator variable and not documented

- Poor document control – inadequate retention periods for documentation
- Unidentified or unexpected laboratory samples analysed for a range of tests - this may be outside the protocol and therefore without consent

A review of existing policies and systems (including organisation-wide policies not specific to research) against these findings will identify areas of work. These should be prioritised using a risk-based approach.

**Recommendation 10: Review your system against the common findings from inspections conducted by the MHRA**

- Test your systems for compliance.
- Document and prepare an action plan for any system development.

## 7 Appendix A: Key definitions

**Adverse Event** Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

**Adverse Reaction** Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

**Chief Investigator** The investigator who takes primary responsibility for the conduct of the trial. If the trial involves multiple sites there will be a principal investigator at each site taking responsibility for their site.

**Clinical trial** Any investigation in human subjects, other than a non-interventional trial, intended -

- to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products,
- to identify any adverse reactions to one or more such products, or
- to study absorption, distribution, metabolism and excretion of one or more such products, with the object of ascertaining the safety or efficacy of those products.

**Insurance or indemnity** The provision for meeting the losses or liabilities of subjects involved in the trial. For commercially-sponsored projects the company should provide indemnity against non-negligent harm.

**Interventional trial** An interventional trial is a trial where the:

- Medicinal Product is prescribed outside the terms of its MA,
- Patient assignment is decided by a protocol,
- Prescription of the IMP is linked to the decision to include the patient in the study,
- Additional diagnostic or monitoring procedures are applied,
- Methods Other than epidemiological methods are being used for analysis of data.

**Investigational medicinal product** A pharmaceutical form of an active substance or placebo being tested, or to be tested, or to be used, as a reference in a clinical trial, and includes a medicinal product which has a marketing authorization but is, for the purposes of the trial:

- used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorization,
- used for an indication not included in the summary of product characteristics under the authorization for that product, or
- used to gain further information about the form of that product as authorised under the authorization;

**Investigator** In relation to a clinical trial, the authorised health profession responsible for the conduct of that trial at a trial site. "Authorised health profession" means:

- doctor
- dentist
- nurse
- pharmacist

**Marketing authorization** means -

- marketing authorization granted by the licensing authority under the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 (a)
- a marketing authorization issued by the competent authority of an EEA State, Other than the United Kingdom, in accordance with Directive 2001/83/EC,
- a marketing authorization granted by the European Commission under Council Regulation (EEC) 2309/93 (b) or
- a product license granted by the licensing authority for the purposes of section 7 of the Medicines Act 1968 (c)

**Medicinal Product** This includes

- (a) any substance or combination of substances presented for treating or preventing disease in human beings
- (b) any substance or combination of substances administered with a view to making medical diagnosis or to restoring, correcting or modifying physiological functions in human beings. A substance can be human, animal, vegetable or chemical.

**Non-interventional trial** Means a study of one or more medicinal products which have a marketing authorization, where the following conditions are met -

- the products are prescribed in the usual manner in accordance with the terms of that authorization,
- the 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,
- the decision to prescribe a particular medicinal product is clearly separated from the decision to include the patient in the study,
- no diagnostic or monitoring procedures are applied to the patients in the study Other than those which are ordinarily applied in the course of the particular therapeutic strategy in question, and
- epidemiological methods are to be used for the analysis of the data arising from the study;

**Serious Adverse Event** Any serious adverse reaction or unexpected serious adverse reaction respectively that

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity or
- consists of a congenital anomaly or birth defect

**Sponsor** An individual, company, institution, or organisation who takes responsibility for the initiation management and financing (or the arranging of the financing) of that trial. (At GOSH / ICH individuals should not agree to take on Sponsor responsibilities or agree to GOSH/ICH being the Sponsor without prior agreement of the R&D office). Sponsor responsibilities could be allocated to different persons or jointly.

**Subject (in relation to a clinical trial)** An individual, whether a patient or not, who participates in a clinical trial:

- as a recipient of an investigational medicinal product or of some Other treatment of product, or
- without receiving any treatment or product, as a control

**Suspected unexpected adverse reaction (SUSAR)** An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out

- in the case of a product with an MA in the summary of product characteristics for that product
- in the case of any Other investigational medicinal product in the investigators brochure relating to the trial in question

## 8 Appendix B: Useful webpages

This is a simple list offering portals to further information and directed links to specific areas of interest.

### Legislation, policy and guidance

The MRC/DH Clinical Trial Toolkit

General guidance for non-commercial organisation conducting research

<http://www.ct-toolkit.ac.uk>, accessed 31 October 2006

The Medicines for Human Use (Clinical Trials) Regulations 2004

[www.legislation.hmso.gov.uk/si/si2004/20041031.htm](http://www.legislation.hmso.gov.uk/si/si2004/20041031.htm), accessed 31 October 2006

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

<http://www.opsi.gov.uk/si/si2006/20061928.htm>, accessed 31 October 2006

The Research Governance Framework for Health and Social Care (Version 2)

[http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/ResearchGovernanceArticle/fs/en?CONTENT\\_ID=4002112&chk=PJlaGg](http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/ResearchGovernanceArticle/fs/en?CONTENT_ID=4002112&chk=PJlaGg), accessed 31 October 2006

Medicines and Healthcare products Regulatory Agency (MHRA) Homepage

<http://www.mhra.gov.uk>, accessed 31 October 2006

### Documents relating to the experience of being inspected by the MHRA

Experience of MHRA inspection from the United Bristol Healthcare NHS Trust

<http://www.rdforum.nhs.uk/confrep/annual05/benton.ppt>, accessed 31 October 2006

Non-Commercial Web Sites Relating to Clinical Trials

United Bristol Hospital NHS Trust (see Information Sheet Index link for guidance documents relating to protocol writing, site file set-up and site file template)

<http://www.ubht.nhs.uk/R&D/>, accessed 31 October 2006

UCL Biomedicines Unit (including annual safety report template)

<http://www.ucl.ac.uk/biomed-r-d/>, 31 October 2006

Leeds Teaching Hospitals NHS Trust

[http://www.leedsth.nhs.uk/sites/research\\_and\\_development/res\\_gov\\_policy.php](http://www.leedsth.nhs.uk/sites/research_and_development/res_gov_policy.php), accessed 31 October 2006

University College London Hospitals NHS Trust / University College London

<http://www.ucl.ac.uk/clinical-trials/>, accessed 31 October 2006

Institute of Child Health

<http://www.ich.ucl.ac.uk/ich/r&d/ctag.htm>, accessed 31 October 2006

Oxford Radcliffe NHS Trust

<http://www.oxfordradcliffe.nhs.uk/research/researchers/policies.asp>, accessed 31 October 2006

Wales Cancer Research Network (including SOPs relating to the investigational site)

[http://www.wctn.org.uk/info\\_for\\_health\\_pros/research\\_governance.htm](http://www.wctn.org.uk/info_for_health_pros/research_governance.htm), accessed 31 October 2006

### Specific links to useful documents and templates

Specific links relating to writing trial protocol

<http://www.ubht.nhs.uk/R&D/Information/Index%20list.htm>, accessed 31 October 2006

[http://www.ucl.ac.uk/biomed-r-d/guides/guide\\_protocol\\_content\\_%20format.doc](http://www.ucl.ac.uk/biomed-r-d/guides/guide_protocol_content_%20format.doc), accessed 31 October 2006

Specific links relating to Trials Master File and Investigator Site File

<http://www.ubht.nhs.uk/R&D/Information/Index%20list.htm>, accessed 31 October 2006

[http://www.ucl.ac.uk/biomed-r-d/guides/template\\_tmf\\_ct%20.doc](http://www.ucl.ac.uk/biomed-r-d/guides/template_tmf_ct%20.doc), accessed 31 October 2006

Specific links relating to safety policies and processes

<http://www.ubht.nhs.uk/R%26D/Policies&SOPs/Research%20related%20AE%20policy%20-%20version%203.1%2025-10-05.pdf>, accessed 31 October 2006

<http://www.oxfordradcliffe.nhs.uk/research/documents/AdverseEventsJan06Version1.pdf>, accessed 31 October 2006

[http://www.leedsth.nhs.uk/sites/research\\_and\\_development/Pharmacovigilance.php](http://www.leedsth.nhs.uk/sites/research_and_development/Pharmacovigilance.php), accessed 31 October 2006

Specific link for an annual safety report and guidance

[http://www.ucl.ac.uk/biomed-r-d/guides/guide\\_asrprep\\_submission.doc](http://www.ucl.ac.uk/biomed-r-d/guides/guide_asrprep_submission.doc), accessed 31 October 2006

Specific link to a sample monitoring policy

<http://www.oxfordradcliffenhs.uk/research/researchers/documents/MonitoringandAuditofResearchProjectsv1.pdf>, accessed 31 October 2006

The MHRA seminar "The Changing Face of Good Clinical Practice" on 15 November 2005

The MHRA held a seminar "The Changing Face of Good Clinical Practice" on 15 November 2005. The conference addressed issues relating to both commercial and non-commercial clinical trials.

This report covers the main points raised during the conference that are relevant to non-commercial clinical trials. The focus of the report is explaining the MHRA inspection process and findings from inspections carried out so far.

[http://www.rdforum.nhs.uk/docs/mhra\\_gcp\\_1105.doc](http://www.rdforum.nhs.uk/docs/mhra_gcp_1105.doc), accessed 31 October 2006

## 9 Appendix C: EU Commission algorithm defining clinical trials within the scope of the Clinical Trials Directive

### IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
<b>A CLINICAL TRIAL OF A MEDICINAL PRODUCT?</b>				<b>A NON-INTERVENTIONAL CLINICAL TRIAL?</b>
<b>Is it a medicinal product (MP)?<sup>i</sup></b>	<b>Is it not a medicinal product?</b>	<b>What effects of the medicine are you looking for?</b>	<b>Why are you looking for those effects?</b>	<b>How are you looking for those effects?</b>
<p>If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.</p> <p>If you answer yes to <u>any</u> of the questions below go to column B.</p>	<p>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</p> <p>If you answer no to this question below go to column C.</p>	<p>If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column D.</p>	<p>If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column E.</p>	<p>If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C &amp; D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.</p>
<p>A.1 Is it a substance<sup>ii</sup> or combination of substances presented as having properties for treating or preventing disease in human beings ?</p> <p>A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</p> <p>A.3 Is it an active substance in a pharmaceutical form?</p>	<p>B.1 Are you <u>only</u> administering any of the following substances?</p> <ul style="list-style-type: none"> <li>• Human whole blood<sup>iii</sup>;</li> <li>• Human blood cells;</li> <li>• Human plasma;</li> <li>• Tissues except a somatic cell therapy medicinal product<sup>iv</sup>;</li> <li>• A food product<sup>v</sup> (including dietary supplements) not presented as a medicine;</li> <li>• A cosmetic product<sup>vi</sup></li> <li>• A medical device</li> </ul>	<p>C.1 To discover or verify/compare its clinical effects?</p> <p>C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</p> <p>C.3 To identify or verify/compare its adverse reactions?</p> <p>C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?</p>	<p>D.1 To ascertain or verify/compare the efficacy<sup>vii</sup> of the medicine?</p> <p>D.2 To ascertain or verify/compare the safety of the medicine?</p>	<p>E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</p> <p>E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?</p> <p>E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol<sup>viii</sup>?</p> <p>E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?</p> <p>E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?</p> <p>E.6 Will epidemiological methods be used for the analysis of the data arising from the study?</p>

---

<sup>i</sup> Article 1.2 of Directive 2001/83/EC is replaced by Article 1.1 of Directive 2004/27/EC which provides the definition of "medicinal product" which applies for the purposes of Directive 2001/20/EC.

<sup>ii</sup> Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.

<sup>iii</sup> This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.

<sup>iv</sup> Somatic cell therapy medicinal products use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means.

<sup>v</sup> Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

<sup>vi</sup> The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.

<sup>vii</sup> Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

<sup>viii</sup> Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.

[http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04\\_2006/clinical\\_trial\\_qa\\_april\\_2006.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2006/04_2006/clinical_trial_qa_april_2006.pdf), accessed 31 October 2006

## 10 Appendix D: Checklist of essential documents for CTIMPs

This guide describes the essential documentation that is required under ICH Good Clinical Practice (ICH GCP). The Clinical Trials Regulations do not require the adoption of ICH GCP but the checklist provides a useful reference. This section will be updated when the specific modalities for non-commercial research are finalised..

### Before the clinical conduct of the trial

ICH GCP Ref.	Topic	Located in Investigator file	Located in file of sponsor
8.2.1	Investigator's Brochure	X	X
8.2.2	Signed protocol and amendments, if any, and sample case report form	X	X
8.2.3	Information given to trial subject Advertisement for subject recruitment	X	X
8.2.4	Financial aspects of the trial	X	X
8.2.5	Insurance statement (where required)	X	X
8.2.6	Signed agreement between involved parties	X	X
8.2.7	Dated, documented approval of Research Ethics Committee	X	X
8.2.8	Research Ethics committee composition	X	X
8.2.9	Regulatory Authority Authorisation (if applicable)	X	X
8.2.10	Curriculum vitae and Other documents evidencing qualifications of investigator(s) and sub-investigator(s)	X	X
8.2.11	Normal values/ranges for medical/lab tests included in the protocol.	X	X
8.2.12	Medical/lab/technical procedures/tests Certification or accreditation; established quality control; Other validation.	X	X
8.2.12	Sample of label(s) attached to medicinal products		X
8.2.14	Instructions for handling of investigational products and trial-related materials (if not in protocol or Investigator Brochure)	X	X
8.2.15	Shipping records for investigational numbers products		X
8.2.16	Certificates of analysis of investigational product shipped	X	X
8.2.17	Decoding procedures for blinded trials	X	X
8.2.18	Master Randomisation List		X
8.2.19	Pre-trial monitoring report		X

## During the clinical conduct of the trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

ICH Ref.	GCP Topic	Located in Investigator file	Located in file of sponsor
8.3.1	Investigator's Brochure updates	X	X
8.3.2	Any revision to: <ul style="list-style-type: none"> <li>• Protocol/amendment(s) and</li> <li>• CRF</li> <li>• Informed consent form</li> <li>• Patient/Parent Information Sheets</li> </ul>	X	X
8.3.3	Dated, documented approval of independent ethical committee of the following: <ul style="list-style-type: none"> <li>• Protocol amendment(s)</li> <li>• Revisions of: Informed consent form- Patient/Parent Information Sheets</li> <li>• Any Other documents where approval required.</li> </ul>	X	X
8.3.4	Regulatory authorities approvals where required	X	X
8.3.5	Curriculum vitae for new investigator(s) and sub-investigator(s)	X	X
8.3.6	Updates to normal values/ranges	X	X
8.3.7	Updates of medical/lab/technical procedures/tests	X	X
8.3.8	Documentation of investigational product	X	X
8.3.9	Certificates of analysis for new batches of investigational product		X
8.3.10	Monitoring visit reports		X
8.3.11	Relevant communication other than site visits Letters inc. printed emails, Meeting reports, Notes of telephone calls	X	X
8.3.12	Signed informed consent forms	X	
8.3.13	Source documents	X	
8.3.14	Signed, dated and completed case report forms	X (copy)	X (original)
8.3.15	Documentation of CRF corrections	X (copy)	X (original)
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	X	X
8.3.17	Notification by sponsor and/or investigator, where applicable, to regulatory authorities of unexpected serious adverse drug reactions and of other safety information	X (where required)	X
8.3.18	Notification by sponsor to investigators of safety information	X	X
8.3.19	Interim or annual reports to independent ethics committees	X	X (where required)
8.3.20	Subject screening log	X	X (where required)
8.3.21	Subject identification code list	X	
8.3.22	Subject enrolment log	X	
8.3.23	Investigational products accountability at site	X	X
8.3.24	Signature sheet	X	X
8.3.25	Record of retained body fluids/tissue samples (if any)	X	X

### After completion or termination of trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

ICH Ref.	GCP Topic	Located in Investigator file	Located in file of sponsor
8.4.1	Investigational product(s) accountability at site	X	X
8.4.2	Documentation of investigational product destruction	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	X	
8.4.4	Audit certificate (if available)		X
8.4.5	Final trial close-out monitoring report		X
8.4.6	Treatment allocation and decoding documentation		X
8.4.7	Final report by investigator to Independent ethics committee where required	X	
8.4.8	Clinical study report	X (if applicable)	X

## 11 Appendix E: Example correspondence

### Example letter: Advance notice of MHRA statutory GCP inspection

It is anticipated that the MHRA Statutory GCP Inspection programme will commence in May 2004. Your organisation has been provisionally scheduled for inspection in the next three months. To this end, please provide the information requested for planning purposes within 21 days of the date of this request.

The Medicines and Healthcare Products Regulatory Agency (MHRA) Inspectorate will contact your organisation regarding specific inspection dates in due course.

Confirmation of inspection dates will be advised in writing and will detail the terms of reference for the inspection and any further inspection-specific requests.

Routine GCP Inspections will examine the systems used by your organisation in the conduct of clinical trial research. This will involve a brief tour of facilities, review of documentation and interviews with key personnel. If appropriate, one or two Investigator sites involved in your current trials may also be inspected of how your organisation's trial procedures were applied.

An outline plan will usually be provided 1 - 2 weeks in advance of the inspection dates. Any comments or clarification required in respect of this plan can be discussed with the Inspectors at this time. Relevant contact details, and further information will be supplied with the Inspection Plan.

Following issue of the Inspection Report for your response, an inspection fee will be charged and you will receive an invoice from MHRA fees section.

If you have any questions concerning this request, please contact the Hitchin office, details above, and your enquiry will be directed appropriately.

Yours sincerely,

### General Requirements

By preference, information should be submitted **electronically** (for example on secure CD-ROM in common industry standard software packages) **with a single hard-copy**. If it is not possible to produce the package in electronic format, please provide **duplicate** hard copies. A list of contents should be included that gives clear document references and the total number of pages for each document supplied (to enable an initial completeness assessment on receipt; i.e. each page need not necessarily be numbered provided this assessment can be made).

Wherever possible, supplement (or replace) text descriptions with simple plans, outline drawings and schematics for illustrative purposes.

### During the Inspection

During the inspection the following should be made available (where applicable):

- Adequate resources such as office space, and use of a photocopier. Please be aware that where a facility is visited by an Inspection Team, interviews may be conducted in parallel; there should be sufficient logistical capacity and support (for example accompanying staff) for this arrangement to be accommodated.
- For trials selected by the MHRA for review: trial related documents including the Trial Master File, Case Report Form (including adverse and serious adverse event /SUSAR reports), ethics committee documentation, drug accountability and reconciliation records.

- CVs, training records, job descriptions for staff involved in clinical trials and related activities (including Quality Assurance). \*
- Policies, SOPs and related working practice documents.
- Quality assurance plans and schedules
- Computer system validation documentation.\*
- Maintenance/service records for relevant equipment including computer systems.

Note 3\*: Specific records will be requested at Inspection.

### **Notes for Completion of the Form (Section 2, overleaf)**

1. Please provide details of the person who will be the key contact for the logistical aspects of the inspection.
2. This information is essential to fee category determination, please use the activity descriptions listed, in preference to any in-house terminology you may currently employ.

If you require an electronic copy of this document please contact the Hitchin Office.

Please note, the following information is requested specifically in relation to your clinical trial work within the UK, and should be provided within 21 days.

### **Section 1: Requested Items**

1. A complete list (or summary) of UK clinical trials from 01 May 2003 which includes completed/historical, ongoing or prospective UK studies (i.e. those which have been approved, but which may not have recruited subjects at this time): Please identify trials which have sites within the UK.

Note 1\*: Where relevant, an Inspector will contact the named personnel (Section 2) to provide further specific information, such as a clinical trial protocol and Other Essential Documents, on selected trials prior to the inspection.

2. Organisation charts with brief summaries of responsibilities (directly related to the activities in Section 2), if not obvious from department/function names.
3. An over-view (with location) of all company facilities located within HieUK involved in clinical trial activities, including key service providers\*, CROs\* and support services\* (as necessary in a generic form).

Note 2\*: We are interested in those service providers that are involved in key efficacy and/or safety processes only, the form appended to this letter gives details of the clinical trial activities of specific interest at this time.

4. A brief (generic) description of archiving arrangements including hard-copy, electronic and investigator site information.
5. A copy of your Standard Operating Procedure (SOP) index and the SOP on production of SOPs
6. Detailed procedures (SOPs) in relation to the following:
  - 6.1. Clinical trial management (from initiation and set-up through to reporting, close- out and archiving).
  - 6.2. Quality Control and Quality Assurance

- 6.3. Computerised systems including purchase, implementation, evaluation/validation, back-up and disaster recovery plans
- 6.4. Equipment maintenance, calibration and servicing routines.
- 6.5. Management/supply of Investigational Medicinal Product (IMP), Commercial and Comparator products within your organisation, and/or directly to the Investigator Site.
- 6.6. IMP handling activities including drug accountability, formulation, dispensing, packaging and labeling routines (if appropriate).
- 6.7. Where applicable, laboratory procedures for method validation, sample chain of custody (receipt to destruction or archiving), kit preparation and logistics.

(Additional SOPs may be requested after receipt of this initial package, to facilitate the inspection process.)

## Section 2

Your Organisation Name & Address																																							
Telephone Number	Fax Number	Web Site Address																																					
Primary Contact <sup>1</sup> Name, Job Title & Address (if different from above)		Direct Telephone Number	E-Mail Address																																				
<p>Please indicate (by deleting as applicable) which activities<sup>2</sup> are performed by your organisation (at the site named above) in the conduct of <b>clinical trials</b>.</p> <table border="0"> <tr> <td>Archiving</td> <td>Yes/No</td> <td>Contract and Agreement Preparation</td> <td>Yes/No</td> </tr> <tr> <td>Project Management</td> <td>Yes/No</td> <td>Use of Computer Systems</td> <td>Yes/No</td> </tr> <tr> <td>Quality System (QA/SOPs)</td> <td>Yes/No</td> <td>Data Management</td> <td>Yes/No</td> </tr> <tr> <td>Training</td> <td>Yes/No</td> <td>Regulatory Affairs (e.g. CTAs, submissions)</td> <td>Yes/No</td> </tr> <tr> <td>Statistics</td> <td>Yes/No</td> <td>Investigational Medicinal Product</td> <td>Yes/No</td> </tr> <tr> <td>Laboratory</td> <td>Yes/No</td> <td>Management</td> <td></td> </tr> <tr> <td>Study Monitoring</td> <td>Yes/No</td> <td>Clinical Trial Pharmacovigilance &amp;/or Safety</td> <td>Yes/No</td> </tr> <tr> <td>Clinical Trial Reporting</td> <td>Yes/No</td> <td>Reporting</td> <td></td> </tr> <tr> <td>Randomisation</td> <td>Yes/No</td> <td>Filing of Essential Documents (Trial Master File)</td> <td>Yes/No</td> </tr> </table>				Archiving	Yes/No	Contract and Agreement Preparation	Yes/No	Project Management	Yes/No	Use of Computer Systems	Yes/No	Quality System (QA/SOPs)	Yes/No	Data Management	Yes/No	Training	Yes/No	Regulatory Affairs (e.g. CTAs, submissions)	Yes/No	Statistics	Yes/No	Investigational Medicinal Product	Yes/No	Laboratory	Yes/No	Management		Study Monitoring	Yes/No	Clinical Trial Pharmacovigilance &/or Safety	Yes/No	Clinical Trial Reporting	Yes/No	Reporting		Randomisation	Yes/No	Filing of Essential Documents (Trial Master File)	Yes/No
Archiving	Yes/No	Contract and Agreement Preparation	Yes/No																																				
Project Management	Yes/No	Use of Computer Systems	Yes/No																																				
Quality System (QA/SOPs)	Yes/No	Data Management	Yes/No																																				
Training	Yes/No	Regulatory Affairs (e.g. CTAs, submissions)	Yes/No																																				
Statistics	Yes/No	Investigational Medicinal Product	Yes/No																																				
Laboratory	Yes/No	Management																																					
Study Monitoring	Yes/No	Clinical Trial Pharmacovigilance &/or Safety	Yes/No																																				
Clinical Trial Reporting	Yes/No	Reporting																																					
Randomisation	Yes/No	Filing of Essential Documents (Trial Master File)	Yes/No																																				
<p><b>Please indicate (by deleting as applicable) which activities are relevant to your organisation but are performed at an alternative location (please specify location(s) and or relevant contact details over-leaf).</b></p> <table border="0"> <tr> <td>Archiving</td> <td>Yes/No</td> <td>Contract and Agreement Preparation</td> <td>Yes/No</td> </tr> <tr> <td>Project Management</td> <td>Yes/No</td> <td>Use of Computer Systems</td> <td>Yes/No</td> </tr> <tr> <td>Quality System (QA/SOPs)</td> <td>Yes/No</td> <td>Data Management</td> <td>Yes/No</td> </tr> <tr> <td>Training</td> <td>Yes/No</td> <td>Regulatory Affairs (e.g. CTAs, submissions)</td> <td>Yes/No</td> </tr> <tr> <td>Statistics</td> <td>Yes/No</td> <td>Investigational Medicinal Product</td> <td>Yes/No</td> </tr> <tr> <td>Laboratory</td> <td>Yes/No</td> <td>Management</td> <td></td> </tr> <tr> <td>Study Monitoring</td> <td>Yes/No</td> <td>Clinical Trial Pharmacovigilance &amp;/or Safety</td> <td>Yes/No</td> </tr> <tr> <td>Clinical Trial Reporting</td> <td>Yes/No</td> <td>Reporting</td> <td></td> </tr> <tr> <td>Randomisation</td> <td>Yes/No</td> <td>Filing of Essential Documents (Trial Master File)</td> <td>Yes/No</td> </tr> </table>				Archiving	Yes/No	Contract and Agreement Preparation	Yes/No	Project Management	Yes/No	Use of Computer Systems	Yes/No	Quality System (QA/SOPs)	Yes/No	Data Management	Yes/No	Training	Yes/No	Regulatory Affairs (e.g. CTAs, submissions)	Yes/No	Statistics	Yes/No	Investigational Medicinal Product	Yes/No	Laboratory	Yes/No	Management		Study Monitoring	Yes/No	Clinical Trial Pharmacovigilance &/or Safety	Yes/No	Clinical Trial Reporting	Yes/No	Reporting		Randomisation	Yes/No	Filing of Essential Documents (Trial Master File)	Yes/No
Archiving	Yes/No	Contract and Agreement Preparation	Yes/No																																				
Project Management	Yes/No	Use of Computer Systems	Yes/No																																				
Quality System (QA/SOPs)	Yes/No	Data Management	Yes/No																																				
Training	Yes/No	Regulatory Affairs (e.g. CTAs, submissions)	Yes/No																																				
Statistics	Yes/No	Investigational Medicinal Product	Yes/No																																				
Laboratory	Yes/No	Management																																					
Study Monitoring	Yes/No	Clinical Trial Pharmacovigilance &/or Safety	Yes/No																																				
Clinical Trial Reporting	Yes/No	Reporting																																					
Randomisation	Yes/No	Filing of Essential Documents (Trial Master File)	Yes/No																																				

<Copy this page, as necessary>

Supporting Site Name & Address		
Telephone Number	Fax Number	Web Site Address
Contact, Name, Job Title & Address (if different from above)		Direct Telephone Number E-Mail Address
Supporting Site Name & Address		
Telephone Number	Fax Number	Web Site Address
Contact, Name, Job Title & Address (if different from above)		Direct Telephone Number E-Mail Address
Supporting Site Name & Address		
Telephone Number	Fax Number	Web Site Address
Contact, Name, Job Title & Address (if different from above)		Direct Telephone Number E-Mail Address

**Example letter: Advance notice to internal researchers conducting CTIMPs**

Dear All,

**Re: Advance Notice of MHRA Statutory Good Clinical Practice Inspection**

I write to inform you that the Medicines and Healthcare products Regulatory Agency will be conducting a statutory inspection at XXXX on DD/MM/YYYY.

The purpose of the statutory inspection is to examine the systems used by XXXX in the conduct of clinical research involving investigational medicinal products (IMPs). We know at this stage that this will involve a tour of the facilities, review of documentation and interviews with key personnel. We do not yet know the level of involvement that will be required from Principal Investigators and their research teams. However, the inspection is statutory and the MHRA will expect all researchers they wish to interview to make themselves available. We will endeavor to facilitate these meetings to be mutually convenient wherever possible. We would be grateful for your support in ensuring the researchers meet their responsibilities with regard to this matter.

We are in the process of informing all researchers who are involved in studies with an investigational medicinal product, relevant support department and all General Managers of the inspection.

We will of course keep you up to date with any developments.

Please do not hesitate to contact me should you have any queries.

Best wishes

**Example letter: Notice to investigators providing the timing of the MHRA Inspection**

Dear

**Re: MHRA Statutory Good Clinical Practice Inspection 5, 6, 7<sup>th</sup> May**

Further to my letter dated 1<sup>st</sup> April 2004, I write to inform you that the following study(ies) was (were) included in the list of Clinical Trials provided to the MHRA in advance of their inspection. According to our records you are the Principal Investigator for the(se) trial(s).

Local ID	Full Title	Principal Investigator

As previously stated, we do not know which studies the MHRA Inspectors will choose to examine. The MHRA have not stated what they will inspect but we anticipate that they will concentrate on whether studies are being run in accordance with Good Clinical Practice guidelines. We recommend that you ensure your studies are being run to this guidance and that all 'essential documents' are filed correctly. The list of 'essential documents' and where they should be filed as defined by ICH GCP is available at <http://www.ich.org/LOB/media/MEDIA482.pdf>.

I would be grateful if you could inform your research team that the above study(ies) may be inspected.

If you have any queries please contact xxxxxx

Yours sincerely

## 12 Appendix F: Examples of MHRA inspection plans

### Example 1

Day One	Proposed start time 8:30	Personnel to be interviewed
<p>Opening Meeting (I1)  <b>Introduction to Inspectors and over-view of inspection plan and procedures.</b></p>	8:30 – 9.00	Open session with the Inspectors for brief introduction to inspection process.
<p><b>Research &amp; Effectiveness Department (I1)</b>            To include:            Over-view of how the Organisation controls trials (from required approvals, through in-life trial review and monitoring, to close-down and archive), trial insurance and indemnity arrangements (Trust, and Trust-Investigator agreements/contracts/honorary contracts), general clinical trial/GCP training, management of Investigational Medicinal Products.</p>	9.00 – 11.30	<p>Over-view of how the Organisation controls trials:            R&amp;D Information Officer. R&amp;D Manager (Governance and Quality).</p> <p>General clinical trial/GCP training:            RDSU Co-ordinator.            R&amp;D Manager (Governance and Quality).</p> <p>Investigational Medicinal Products:            Quality Assurance Manager, Pharmacy.            Director of Pharmacy</p>
<p><b>Archiving of (Clinical Trial) Patient Records (I2)</b>            Visit to Medical Records Department – plus visit to supplementary areas for children’s and surgery records (time permitting).</p>	11:30 – 12:30	<p>Medical Records:            Assistant Health Records Manager</p> <p>Children’s –Patient Services Manager            Surgery –Medical Records Supervisor</p>
<b>Lunch and Document Review</b>	12.30 – 13.15	

Day One	Proposed start time 8:30	Personnel to be interviewed
<b>Pharmacy Facilities (I1)</b> Visit to the pharmacy for an over-view of general receipt, management, storage and disposal (or Otherwise) of clinical trial supplies. Selected record/supply review for nominated trials.	13:15 – 14:30	Pharmacy Technician  Supporting/Available: Pharmacy Manager (Oncology & Aseptic Services) <b>Chief Pharmacist, BCH Pharmacy</b>
<b>Information Technology (I2)</b> Over-view of organisation information management systems that will handle data from clinical trials – access, authorisation/approval processes, record storage, transfer, back-up etc.	14:30 – 15:15	Director of IM&T.
<b>Document Review</b> Review of trial master file, case report forms, medical records etc for first selected trial.	15:15 – 17:30	Principal Investigator Clinical Trials Unit Manager, Research Nurse Trial Coordinator
Inspectors: SOP copies should be made available in the office to be used by the inspection team. CVs, job descriptions and training records (as applicable) should be made available for the personnel interviewed and may be requested for Other personnel. <b>The times and activities listed above are provisional and may be adjusted during the inspection.</b>		

Day Two	Proposed start time 8:30	Personnel to be interviewed	
Facility Tour and Investigator Meeting (I2) <b>To be included in the session:</b> Tour of facilities to focus upon key areas which the clinical trial subjects encounter e.g. treatment rooms and specific diagnostic areas. Storage areas for investigational medicinal product (if applicable), clinical trial records/data, clinical trial samples etc. <b>Meeting with the Principal Investigator (est 30 – 45 min)</b> <b>Meeting with designated research staff</b> <b>Review of trial-specific records and diary/appointment information.</b> Feedback of findings dependent upon availability of P.I to attend closing meeting (10 -15 minutes at session close)	8:30 – 12.00	As directed by requirements of the session:  Principal Investigator Clinical Trials Unit Manager Research Nurse Trial Coordinator	
<b>Lunch and Document Review</b>	12.00 – 13.00		
<b>PLEASE NOTE PARALLEL SESSIONS</b>			
Facility Tour and Investigator Meeting (I2) <b>Session requirements as per previous</b>	As directed by requirements of the session:  Principal Investigator Research Nurse.	13.00 – 17.00	Facility Tour and Investigator Meeting (I1) Session requirements as per previous  As directed by requirements of the session: Principal Investigator Research Staff
<b>Inspectors Review Meeting</b> Review of inspection progress	17:00 – 17:30		
Inspectors: SOP copies should be made available in the office to be used by the inspection team. CVs, job descriptions and training records (as applicable) should be made available for the personnel interviewed and may be requested for Other personnel. <b>The times and activities listed above are provisional and may be adjusted during the inspection.</b>			

Day Three	Proposed start time 8:30	Personnel to be interviewed
Tour of Laboratories <b>Brief visit to areas which perform clinical trial sample analysis (Haematology, Clinical Chemistry, Microbiology)</b> Note – these sessions may be conducted in parallel to facilitate inspection timings	8:30 – 10.00	Haematology –Head Biomedical Scientist Clinical Chemistry –Chief MSO Microbiology –Acting Deputy Head MLSO
<b>Tour of Radiology/Imaging Specialists (Outside the Oncology CTU)</b> Visit to clinical trial supporting areas involved in key safety and efficacy variables.	10.00 – 11.00	Professor of Radiology. Superintendent radiographer (CT)
<b>Outstanding Issues</b> Resolution of outstanding items	11:00 – 12:00	As appropriate from inspection proceedings (to be highlighted at previous sessions.)
<b>Lunch and Document Review</b>	12.00 – 14.00	
<b>Closing Meeting (I1)</b> Presentation of inspection results including preliminary categorisation of any findings.	14.00 – 15:00	Session open to inspection participants.
Inspectors: SOP copies should be made available in the office to be used by the inspection team. CVs, job descriptions and training records (as applicable) should be made available for the personnel interviewed and may be requested for Other personnel. <b>The times and activities listed above are provisional and may be adjusted during the inspection.</b>		

## Example 2

DAY1	PROPOSED TIMES	STAFF
Introduction with Senior Executive and Associated Staff	9am – 10am	As appropriate
Medical Records & Archiving of Records	10am –11am	Head of Medical Records and IT Manager
PHARMACY FACILITIES FOR CLINICAL TRIALS. Review facilities, procedures and records in main pharmacy and in Sterile Unit. Check on drug accountability for chosen trials.	11:15am –12:15am	Pharmacy Staff
Lunch	12:15 – 1:15	
R&D Office Overview of how organisation controls trials, Indemnity & insurance for trials, Review records of indemnity & agreements between Trust, University and Investigator. Regulatory approval e.g. CTA/DDX	1:15 – 3:00 RVI	Research Governance Manager and Head of R&D
Break and travel	3:00-3:30	
Pharmacy – Oncology	3:45 – 5pm Newcastle General Hospital	Cytotoxic preparation staff
DAY 2		
INSPECT FACILITIES AND RECORDS OF 1 <sup>ST</sup> CHOSEN TRIAL. INTERVIEW STAFF INVOLVED WITH TRIAL.	About 3.5 hours	Trials staff
<b>Two inspectors move to 2<sup>nd</sup> &amp; 3<sup>rd</sup> Trials at 10:45am.</b>		
INSPECT FACILITIES AND RECORDS OF 2 <sup>nd</sup> & 3 <sup>rd</sup> CHOSEN TRIALS. INTERVIEW STAFF INVOLVED WITH TRIAL. Give feedback to investigator (could be done in closing meeting on 4th day)	About 3. 5 hours	Trials Staff
DAY 3		
Option to return to resolve outstanding issues in trials inspected on day 2.	(morning)	
IT demonstration (RVI)	9 – 11 am	IT Manager
University issues/perspective (RVI) Pathology (RVI) (Clin. Chem and haematology).	11- 12noon	Assistant Registrar

Imaging Dept. (NGH)	12 –1pm Travel 1:15 – 2:30pm to include lunch	Laboratory staff
Further trial related issues	3 –5pm	Imaging Staff Relevant staff
<b>DAY 4</b>		
Closing meeting	11am	Attendance to be as organisation require

## 13 Appendix G: Membership of the working group

### Working Group

- Phillip Smith (Chair), Ipswich Hospital NHS Trust
- Christine McGrath, Southampton University Hospitals NHS Trust (previously at United Bristol Healthcare NHS Trust)
- Jane Varey, Newcastle upon Tyne Hospitals NHS Trust
- Tanya Symons, Freelance GCP Trainer and Consultant
- Susan Kerrison, University College London Hospital NHS Trust
- Nick McNally, University College London Hospital NHS Trust
- Emma Tucker, Oxford Radcliffe NHS Trust
- Emma Pendleton, Institute for Child Health / Great Ormond Street Hospital
- Louise Forster, Institute for Child Health / Great Ormond Street Hospital
- Joanna Galea-Lauri, Institute for Child Health / Great Ormond Street Hospital
- Helen Cadiou, Institute for Child Health / Great Ormond Street Hospital
- Sara Shankland, Velindre NHS Trust
- Stephen Lock, North Yorkshire Research and Development Alliance
- Sarah Bathers, Cancer Research Clinical Trials Unit, University of Birmingham

### Acknowledgements

The content of this guidance arose from discussions by the working group (Dec 2005 and Jan 2006) and was edited by Phillip Smith and Tanya Symons from the working group and Janet Messer (NHS R&D Forum). The content is based on text provided by:

- Christine McGrath (Southampton University Hospitals NHS Trust)
- Dr Jane Varey (Newcastle upon Tyne Hospitals NHS Trust)
- Tanya Symons (GCP Trainer and Consultant)
- Dr Helen Cadiou (Clinical Trials Co-ordinator, R&D GOSH/ICH)
- Dr Louise Forster (Research Governance Co-ordinator, GOSH/ICH)
- Dr Joanna Galea-Lauri (Clinical Trials Co-ordinator, GOSH/ICH)
- Miss Emma Pendleton (Head of R&D, GOSH/ICH)
- Stephen Lock (R&D Manager, North Yorkshire R&D Alliance)
- Tomasz Kurdziel (University of Leeds/ Leeds Teaching Hospitals NHS Trust)

Meetings were kindly hosted by GOSH/ICH.

Tanya Symons kindly provided Appendices I & H.

The document is a product of the NHS R&D Forum Research Governance Working Group .

### Disclaimer

This document has been developed to share experiences of organisations that have been inspected by the MHRA. It is not intended to replace information or advice from the MHRA or legal advisers. Please consult the MHRA for up to date information.

## **14 Appendix H: A Summary of Changes Impacting on Non-Commercial Sponsors and Investigators arising from the amendment to 'The Medicines for Human Use (Clinical Trials) Regulations 2004'**

This section has been written by Tanya Symons.

### **14.1 Introduction**

The Medicines for Human Use (Clinical Trials) Regulations 2004 (known as the Clinical Trials Regulations) transposed the EU Clinical Trials Directive into UK law. In 2005 the European Commission published a further Directive (2005/28/EC) known as the GCP Directive. The MHRA has chosen to implement the requirements of the GCP Directive by amending the current Clinical Trials Regulations. The Medicines for Human Use (Clinical Trials) Amendment Regulations (the Amendment Regulations) were laid in Parliament on 20 July 2006 and will come into force on 29 August 2006. The Amendment Regulations also include additional changes to the Clinical Trials Regulations which do not arise out of the GCP Directive. These additional provisions relate to arrangements for payment of fees; notifying the licensing authority of serious breaches of GCP and/or the protocol; and the extension of the infringement notices (warning notices) regime.

The main amendments which impact non-commercial sponsors relate to:

- a) Sponsor's delegation of functions
- b) Content and presentation of the investigator's brochure
- c) Retention of documents and archiving
- d) Wording of principles of Good Clinical Practice
- e) Serious breach of GCP or protocol
- f) MHRA power to inspect studies not holding a CTA

Link to the Amendment Regulations:

<http://www.opsi.gov.uk/si/si2006/20061928.htm>, accessed 31 October 2006

### **14.2 Sponsor's Delegation of Functions**

The Amendment Regulations confirm that a sponsor can delegate some or all of its functions but retains the responsibility for those functions.

Implication: Non-commercial sponsors should have a good oversight of any functions delegated.

For example if the chief investigator or trial team take on most aspects of the management of an individual trial, the sponsor should be able to satisfy themselves of the following:

- Are all approvals in place?
- How GCP compliant is the trial?
- Is safety information being captured and reported?
- What is the process for ensuring relevant bodies are notified of trial end within required timelines?

### **14.3 Content and Presentation of the Investigator's Brochure**

The Amendment Regulations stipulate that the sponsor must ensure the investigator brochure is validated and updated at least once a year. However, as most non-commercial trials involve IMPs that are already marketed in the UK (or other EU countries); the SmPC often replaces the investigator brochure. The MHRA have clarified that the requirement to update applies to the investigator brochure and not the SmPC that replaces it.

### **14.4 Retention of Documents and Archiving**

The Amendment Regulations confirm that a sponsor must:

- keep a trial master file which should be made readily available for inspection or audit at all reasonable times and contain all relevant essential documents
- ensure the trial master file and medical records are retained for at least 5 years

N.B. It is expected that commercial sponsors will require the retention of records for longer periods to comply with ICH GCP

- appoint named individuals to be responsible for archiving and restrict access to archived documents to these individuals

The Amendment Regulation confirm that ethics committees must retain documents for at least 3 years after completion of the trial

The European Commission have published further draft guidance on the requirements for the content of the Trial Master File and Investigator Site File and the specific modalities that may be adopted for non-commercial trials:

(<http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm>, accessed 31 October 2006):

- A compilation of legislative and guidance documents for clinical trials "Volume 10 – Clinical Trials"
- Consultation on draft guidance for specific modalities for non-commercial clinical trials

#### **14.5 Wording of the Conditions and Principles of Good Clinical Practice**

The MHRA have amended the wording of the conditions and principles of GCP to make them consistent with Articles 2 to 5 of the GCP Directive. Two new principles (7 and 8) are highlighted in red.

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.
7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

#### **Conditions based on Article 3 of the Directive**

10. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.

11. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified

dentist.

12. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

13. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998 are safeguarded.

14. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor which may arise in relation to the clinical trial.”

#### 14.6 Serious Breach of GCP or Protocol

This amendment requires the sponsor to notify the MHRA within 7 days whenever the sponsor becomes aware of ‘serious breaches’ involving:

- a) the conditions and principles of GCP
- b) the protocol relating to that trial

A ‘serious breach’ is defined as a breach which is likely to effect to a significant degree:

- a) the safety of the patient
- b) the scientific value of the trial

Examples of a serious breach of GCP may include:

- Violations of eligibility criteria such that patients are put at risk, or the trial design is invalidated
- Routinely failing to follow instructions for handling trial medication
- Systematically using incorrect patient information and/or consent forms
- Routinely failing to follow safety instructions given in the protocol
- Routinely failing to adhere to data recording/handling instructions given in the protocol

The MHRA will publish further guidance on serious breach in due course.

Information on how to report a serious breach is provided on the MHRA website, [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeId=136](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=136), accessed 31 October 2006.

COREC confirm that the main REC will also require notification in the same timelines

#### 14.7 MHRA Power to Inspect Studies Not Holding a CTA

The amendment gives the MHRA powers to inspect trials not holding a CTA (when they should have them) to establish that they are clinical trials and to require suspension of such trials until all necessary approvals are obtained. The amendment provides for the MHRA to issue infringement notices in such circumstances.

If there is doubt over the trial in relation to whether it is a CTIMP, guidance may be sought from the MHRA Clinical Trials Unit:

[clintrialhelpline@mhra.gsi.gov.uk](mailto:clintrialhelpline@mhra.gsi.gov.uk)

It is recommended records of this correspondence are retained.

## 15 Appendix I: MHRA Inspection Findings: One Year On. Summary of Common Threads and Feedback from Recently Inspected Non-Commercial Sponsor Organisations

Prepared by Tanya Symons (T Symons Associates Ltd.) - Oct 2007

In a recent symposium, the MHRA confirmed that to date, 13 NHS Trusts have undergone routine systems inspections in 2006/7. Members of the R&D Forum Research Governance Working Group have received feedback from a sample of these inspections. This document aims to highlight some of the common threads and emerging messages that have arisen from this sample of sponsor inspections.

The three main areas of finding that appear to be common place are as follows:

### 1) IMP Management

**Overview: Failure to understand and implement the legislative requirements for an Investigational Medicinal Product (IMP).**

In particular, systems for ensuring an IMP is manufactured, imported, packaged, labelled and distributed in accordance with The Medicines For Human Use (Clinical Trials) Regulations (SI 2004 1031) and Good Manufacturing Practice (GMP) requirements.

Limited examples include:

- Failure to set up robust systems to ensure green light procedures for drug release are in place so that the sponsor organisation can be sure this activity is regulatory compliant.
- Failure to confirm clarity of roles and responsibilities (e.g. ensuring appropriate technical agreements are in place with IMP suppliers).

### 2) Quality Systems

**Overview: Absence of supporting procedures to ensure that the Sponsor's obligations are met when functions are delegated.**

In particular, when tasks are delegated to Chief Investigators, absence of assurances and checks (quality assurance and quality control procedures) to ensure these tasks are being performed in accordance with regulatory requirements on the sponsor's behalf.

Limited examples include:

- Robust systems to ensure Chief Investigators understand and comply with pharmacovigilance reporting requirements (Regulation 32 to 35 of SI 2004 1031)
- Sponsor review/oversight of contracts made by investigators with third parties to ensure these are assessed in relation to GCP and sponsor indemnity for clinical trials.
- Documented procedure for signal detection and notification of serious breaches in GCP - Reg. 29a of The Medicines for Human Use (Clinical Trials) Amendment Regulations (SI 2006 1928).  
[See web link below for MHRA guidance on 'Notification of Serious Breaches of GCP/Protocol' \(Word document\)](#)
- Sponsor involvement/oversight in the process to confirm whether amendments are substantial or non-substantial and workable systems to ensure all substantial amendments have all the required approvals before being implemented.
- Systems to ensure quality and credibility of data produced in non-commercial sponsored trials. In particular, can the following questions be adequately answered?
  - Is the database "fit for purpose"?
  - What statistical input has there been?
  - What quality control and quality assurance steps have been implemented from data capture/entry to through to data analysis to report production/publication?

- How have these been documented into order to demonstrate that the data management process culminates in the production of accurate, verifiable and retrievable data?

### Multi-centre Trials

It is important to be aware that as soon as a trial becomes multi-centre, the complexity of the management and the task of maintaining oversight increase many-fold.

Examples of activities that may help to ensure adequate oversight include:

- Contact/site agreement with clarity of roles and responsibilities
- Oversight of the site selection process
- Assessment of, and communication with, site pharmacies to ensure they comply with all legislative requirements for IMP. For example oversight to ensure/confirm that an IMP is not being supplied outside of what was authorised in the CTA (including conditions and remarks)

### 3) Pharmacovigilance

**Overview: Failure to ensure Trust Pharmacovigilance Systems meet the requirements of Regulation 32 to 35 of the Medicines for Human Use Clinical Trials) Regulations (SI 2004 1031).**

The sponsor has a duty to notify to all relevant bodies any event “likely to affect the safety of subjects”. Developing appropriate quality systems for recording, assessing, reporting and managing adverse events is essential to achieve this requirement.

Limited examples of MHRA findings include:

- Failure to ensure systems take into account trend analysis and other signal detections systems such as follow-up of pregnancy until outcome.
- Failure to ensure annual safety reports assembled by Chief Investigators are reported within required timeframes (e.g. CTA anniversary dates tracked on R&D database to signal that the report is due).
- Failure to ensure policies for PV detail provisions for unblinding of SUSARs before reporting to the MHRA/ethics.

#### A note on safety reporting policies:

It is important to ensure that any policy that is implemented is tested to ensure it is robust and can be followed by all who are required to use it. For example, mechanisms for training/awareness of such policies during trial set up will ensure that investigators and their staff (especially if they are delegated sponsor functions for PV) have a good working knowledge of the Trust’s requirements and responsibilities.

### Guidance for Formulating Responses to GCP Inspection Findings

The MHRA have published guidance to give assistance to sponsors formulating the response to their MHRA inspection report to ensure that this post-inspection activity is handled as efficiently as possible.

See link below for the PDF Document titled: [‘Guidance for Formulating Responses to GCP Inspection Findings’](#).

The document highlights the need for all findings to be assessed by the sponsor to determine their root cause and also whether the finding is systematic (i.e. could affect other trials) or isolated.

Responses should be formatted to illustrate the corrective and preventative actions that the Sponsor intends to implement to avoid similar findings in the future. Organisations will be assessed (at the time of their next inspection) whether these corrective and preventative actions have been addressed.

The following web link to the MHRA GCP page includes all the relevant links to the statutory instruments and guidance documents:

MHRA Good Clinical Practice Page:

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeId=136](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=136)