



Research and Development Forum

How to prepare for an inspection for Good Clinical Practice by the Medicines and Healthcare products Regulatory Agency (MHRA): a guide for organisations that sponsor or host non commercial 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.

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Please destroy all previous versions

www.rdforum.nhs.uk

Executive Summary

This guidance has been prepared for organisations sponsoring or hosting non-commercial clinical trials of medicinal products,, 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 all previous documents and incorporates comments and feedback from the MHRA.

This document provides guidance and practical advice on:

- The obligations on non commercial organisations 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.

Disclaimer

This document has been developed to share experiences of non commercial organisations that have been inspected by the MHRA. It is not intended to replace information or advice from the MHRA or legal advisers. It is recommended that you check the MHRA website and other reference websites on a regular basis in the event of any related updates.

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1. Introduction

1.1 Why Research is Important

Regulation should safeguard patients and facilitate research. Patients, the public and researchers have a common interest in ensuring that research is conducted safely and effectively. In this report, we argue that the application of regulation should be both proportionate and symmetrical. A 'one size fits all' approach to regulation damages us all. Instead, regulation of health research should be proportionate to the risks and benefits to individuals and society. Those involved with regulation and governance must recognise that the current approach is asymmetrical; approving an inappropriate study is clearly unacceptable, but delaying or prohibiting an appropriate study harms future patients as well as society as a whole. We propose that the UK's regulation and governance framework around health research should be underpinned by the following principles:

- To safeguard the well-being of research participants.
- To facilitate high-quality health research to the public benefit.
- To be proportionate, efficient and coordinated.
- To maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency.

The EU Clinical Trials Directive (2001/20/EC) was transposed into UK Law by the Medicines for Human Use (Clinical Trials) Regulations 2004, and subsequent amendments. This Clinical Trials Regulations regulate the conduct of Clinical Trials of Investigational Medicinal Products (CTIMPs). As a result, non commercial 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.

Inspections are a normal part of the research regulations – everyone will be inspected at some point, for some it was sooner (based on the 'volume' and 'extent' of their research activities, for others, who only host or are involved in a small number of studies it will be later. Although it can be daunting to have someone closely scrutinising your work, the process is intended to be a constructive, unbiased evaluation of the level of compliance you are achieving within and across your studies, within and between departments/divisions and within and between sites. This guide is intended to be a useful support for you preparing for that inspection.

1.2. Is my study a clinical trial?

The regulations only apply to trials of medicinal products. These are substances or combinations of substances which either prevent or treat disease in human beings or are administered to human beings with a view to making a medical diagnosis or to restore, correct or modify physiological functions in humans.

A clinical trial is an investigation in human subjects which is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, identify any adverse reactions or study the absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products. This definition includes pharmacokinetic studies.

Clinical studies involving only medical devices, food supplements or other non-medicinal therapies (such as surgical interventions) are not covered by the Directive. The regulations do not apply to non-interventional trials. In such trials, no additional diagnostic or monitoring procedure should be applied. Epidemiological methods should be used for the data analysis.

To find out if your study is covered by the EU Clinical Trials Directive or not, use the algorithm 'Is it a clinical trial of a medicinal product?' in Appendix C of this document.

If after using the algorithm, you are still unsure whether or not the clinical study is covered by the Directive then contact the MHRA clinical trial helpline.
clintrialhelpline@mhra.gsi.gov.uk

Remember to keep a record of the response received as this may be looked at on inspection

2. New Notification Scheme for Clinical Trials

The MHRA launched its new notification scheme on 1st April 2011 for medicinal products. This scheme is available for trials authorised in any EU Member State if:

- They relate to the licensed range of indications, dosage and form
- Or, if they involve off-label use (such as paediatrics and oncology etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines.

The Notification Scheme will be open to trials meeting the above criteria and may include randomisation of subjects to different marketed products or repackaging and/or re-labeling of the marketed product(s). Placebo controlled trials will not be open to the notification scheme, nor will trials in which the marketed product has been modified, for example by over-encapsulation

As this is a new scheme it may be subject to change. Please ensure you check the MHRA website on a regular basis. For further details see:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Submittinganotificationforatrial/index.htm>

Following receipt of a valid notification submission, sponsors will receive an acknowledgement letter to say that the trial may go ahead after 14 days from receipt of the notification, if the MHRA has not raised any objections. This means that the acknowledgement letter will act as the authorisation.

If the MHRA raises an objection to the notification, the submission is treated as a standard request for authorisation and an assessment is carried out in the usual way with a time line of 30 days from the receipt of the original notification.

A risk assessment based on the potential risks associated with the use of the investigational medicinal product (IMP) should be made by the sponsor. Background documentation on how to do this is provided on the web site in the new section on the Notification Scheme.

3. MHRA – *who they are*

The Medicines and Healthcare products Regulatory Agency (MHRA) was set up in April 2003 from a merger of the Medicines Control Agency and the Medical Devices Agency. The MHRA is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe. The MHRA is an executive agency of the Department of Health, and has the main aim of protecting, promoting and improving public health.

The GCP Inspectorate within the MHRA are the people responsible for ensuring trials are conducted to the UK Clinical Trials Regulations. There are 15 GCP inspectors covering the whole of the UK including both expert and senior GCP inspectors. The GCP team has a variety of backgrounds (both commercial and non-commercial) giving a broad range of knowledge and experience. Many of the inspectors have also been inspected themselves by the MHRA prior to joining the Agency, so have a good understanding of the needs and constraints of those being inspected.

All GCP inspectors undergo a formal training programme and are educated, at a minimum, to relevant university graduate level (as required by Directive 2005/28/EC and the associated Eudralex Volume 10 guidance). New inspectors are trained through a combination of classroom training and accompanying accredited inspectors on inspections. The programme also includes training in the national and European guidelines for inspection, the systems needed to conduct clinical trials to GCP, and methods for evaluation and reporting of inspection findings. As well as national routine inspections, GCP inspectors are also trained in European Medicines Agency and bioequivalence inspections, and perform requested inspections on their behalf both in the UK, EU and beyond. The MHRA GCP

inspectors are regularly internally assessed to ensure the standards of competence and consistency required are maintained, as well as undergoing external standards audits such as BEMA and ISO.

Outside of inspection the inspectors are also involved in non-commercial training and process development activities. This includes regular meetings with other agencies involved in clinical trials such as NRES and GTAC to ensure streamlining of processes, presenting at requested training events and provision of symposia to the non-commercial sector, providing input and review to the DoH RSS national procedures and NIHR training programme, coordination of the GCP Consultative committee, developing internal and external guidance as new areas of regulations emerge, and working closely internally with other MHRA divisions such as the Clinical Trials Unit and Licensing Assessors.

3.1 MHRA – Aims and Activities

Aims:

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people.

Activities:

- assessing the safety, quality and efficacy of medicines, and authorising their sale or supply in the UK for human use
- overseeing the UK Notified Bodies that audit medical device manufacturers
- operating post-marketing surveillance and other systems for reporting, investigating and monitoring adverse reactions to medicines and adverse incidents involving medical devices and taking any necessary action to safeguard public health, for example through safety warnings, removing or restricting the availability of products or improving designs
- operating a proactive compliance programme for medical devices
- operating a quality surveillance system to sample and test medicines and to address quality defects, monitoring the safety and quality of imported unlicensed medicines and investigating Internet sales and potential counterfeiting of medicines
- regulating clinical trials of medicines and medical devices
- monitoring and ensuring compliance with statutory obligations relating to medicines and medical devices through inspection, taking enforcement action where necessary;
- promoting good practice in the safe use of medicines and medical devices
- managing the General Practice Research Database (GPRD) and the British Pharmacopoeia (BP) and contributing to the development of performance standards for medical devices; offering scientific, technical and regulatory advice on medicines and medical devices
- providing the public and professions with authoritative information to enable informed dialogue on treatment choices. These activities are supported by our ten divisions who are also responsible for: information management
- providing executive support services; human resources; and finance.

4. GCP Risk Based Inspection Process

The GCP inspectorate has always used a risk-based inspection process for the routine statutory inspection programme; in May 2009 the compliance report system was launched to further inform the risk-based programme. This process uses a combination of information provided to the MHRA on the Compliance Report, internal information about previous inspection history, organisational changes and other compliance reports with the results of intelligence gathering to determine an organisation's control of their risk.

The resulting risk assessments are categorised into high, medium and low risk, and inspections prioritised for the organisations with the highest risk category. What this means in practice is that those organisations with a higher risk rating will be inspected more frequently than those with a lower risk rating. Information provided in the compliance report will also be used to determine the approximate amount of inspection time required to conduct the inspection, which will be confirmed once the inspection dossier has been reviewed.

The outcome of the risk assessment will be provided to the organisation. If you have concerns regarding the risk assessment these should be sent to the GCP risk-based inspection mailbox: gcp riskbasedinspections@mhra.gsi.gov.uk. For up to date information see:

www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Riskbasedinspections/index.htm

Completion of the Compliance Report by sponsors, contract research organisation (CROs) or hosting sites is not mandatory. These organisations, however, should be aware that failure to submit a completed Compliance Report will result in being assigned to a high-risk category. Currently, phase 1 units, clinical laboratories and individual investigators not acting as sponsors of clinical trials are not required to complete a Compliance Report.

4.1 Types of GCP Inspection

Three types of GCP inspection are currently undertaken: the routine inspection, the requested inspection, and the triggered inspection. The majority of inspections are routine inspections, carried out as part of the national statutory inspection programme. Routine inspections are an open process where there is open communication between the lead inspector and the inspected organisation.

Triggered inspections relate to information received regarding, for example, data credibility and/or patient safety issues, which when investigated may require an inspection to answer specific questions. Requested inspections take place in response to regulatory applications (both national MHRA applications and European Medicines Agency coordinated applications) where inspections may be required to confirm that related trials have been conducted in accordance with GCP. Triggered inspections may be study-specific or system-based. The process and procedures followed during a triggered inspection are developed on a case-by-case basis by the lead GCP inspector and will be discussed with the organisation concerned at the time.

This guide therefore, will focus on the statutory routine inspections, which fall into the following categories:

4.2 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 ensure 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. There may also be an investigator site inspection included as part of the main sponsor inspection, to review the trial in more detail at one of the sites hosting the sponsored trial. There is usually approximately 6 weeks notice given to the investigator site prior to the inspection, and the timeline for the report starts after the last day of the final site inspection.

4.3 Investigator site inspection

Where the organisation is a host 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 reviewed to ensure that they are "fit for purpose" (e.g. Pharmacy, laboratories).

Note: GCP inspection procedures may be subject to change from time-to-time; MHRA Inspectors have SOPs too, and the inspections will be taken in-line with current procedures, practice and guidance. There are a number of ways that Inspectors are trained to ensure that the comments they make and decisions taken on inspection are as consistent as they can be – it's not unusual on inspection for something to come-up that will need further discussion – don't be worried about this, providing the information requested will help Inspectors and others at the MHRA reach an appropriate conclusion about your study, systems and/or your circumstances. 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. If on receipt of the inspection notification letter you have any questions on the process, the lead inspector will be happy to talk this through with you at the time.

Information from the MHRA on GCP inspections is provided on the MHRA website:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Theinspectionprocess/index.htm#5>.

5. 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.

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.

6. 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.

What GCP means in practice:

- research teams will have a clear description of what the trial is, what its objectives are, and when and how key assessments and measurements will be taken and recorded.
- in advance of the study you will know what data and results will be available when, and how they will be interpreted, analysed and assessed, prior to final publication and reporting.
- anyone, retrospectively, should be able to review the records kept for a study and determine for themselves that the decisions made and results reported are complete, accurate and unbiased. These results can be assessed both in terms of the participants of the studies (and considerations made for them) and the end integrity of the results and conclusions.
- specific roles and responsibilities are defined to ensure these activities take place in a planned and co-ordinated manner before, during and after the conduct of the trial.
- the Sponsor is to oversee these processes and ensure that they are transparent (usually through documentation) at each stage of the trial (before, during and after).
- the Sponsor's responsibilities may be delegated, but this should be done in writing and evident prospectively in the documentation.

- the inspection process examines the systems and procedures in place to ensure that the regulations and GCP are complied with, and therefore necessarily involves documentation review, but also discussion with key staff and questions and queries to elucidate those aspects of the processes which are not self-evident from the records kept.

6.1 Conditions and Principles of Good Clinical Practice for CTIMPs¹

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 from those of ICH GCP to those of the Clinical Trials Directive (2001/20/EC) and brought about the addition of two new principles - 7 and 8 based on requirements of the European Clinical Trials Directive.

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.

¹ From the updated Medicines for Human Use (Clinical Trials) Amendment Regulations 2006

7. The requirements on non-commercial organisations acting as sponsor

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

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

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. 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.²

Note – risk adaption and risk-based approaches to clinical trials are currently in development, these most significantly impact on areas such as monitoring and audit, and organisations should not be afraid to document prospectively their justification for adopting a particular approach to review, oversight, monitoring and audit of a trial. Inspectors acknowledge there is no 'one size fits all' approach, and during inspections review what risks you have assessed and how in practice you are mitigating and monitoring for them to ensure that patients are safe-guarded and that the integrity of the trial results are not compromised.

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, 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, accessed 31 October 2006

7.1 Delegation of Sponsor Responsibilities

The UK Clinical Trial Regulations state:

"Sponsor means, in relation to a clinical trial, the person who takes responsibility for the initiation, management and financing (or arranging the financing) of that trial." The Medicines for Human Use (Clinical Trials) Regulations 2004. Part 1, section 3.

Under current regulation the sponsor has the ability to delegate some or all of their responsibilities to another party so long as there are clear arrangements in place. It is important to note that although delegated, the sponsor remains responsible for the overall regulatory compliance and oversight of the clinical trial as legal responsibility cannot be delegated. For non-commercial organisations the majority of sponsor responsibilities are usually delegated to the Chief Investigator as they are the appropriate person to have direct and continuous oversight of the trial activity.

The table below outlines the common division of responsibility as defined in clinical trial regulations. It is usual in non-commercial organisations that the sponsor will allocate the operational side of their responsibility to the Chief Investigator whilst having compliance systems in place to monitor activity and ensure that regulation is being complied with. Dependent on the set up within your organisation, some of the sponsor activities will be delegated to the Chief Investigator.

The key message here is to ensure that responsibilities between the sponsor and the CI are documented and clear to all parties. In addition all decisions made around sponsorship should be documented.

² 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, accessed 31 October 2006)

SPONSOR	INVESTIGATOR
Approvals MHRA submission Amendment notification and annual updates End of trial notification Funding Contractual arrangements	Approvals Ethics submission Ethics amendments and annual updates NHS site approvals Other approvals as required
Compliance Trial audit and monitoring GCP/Regulatory Compliance IMP/Device supply and manufacture Operational procedures Urgent safety measures Training Serious Breaches Notification	Compliance Patient safety Informed consent Urgent safety measures Day to day monitoring Data collection and management Study management Study specific training
Pharmacovigilance and safety Recording and reporting serious adverse events Expedited safety reporting to competent authority and ethics committee Safety compliance Insurance and indemnity	Pharmacovigilance and safety Reporting serious adverse events to sponsor Providing urgent information for expedited reporting Clinical decisions and urgent safety measures Health and Safety compliance

This has implications for the trial record-keeping, and it may be that the 'Trial Master File' and 'Investigator File' for the study are combined, reducing the need to keep records in duplicate. Organisational procedures should make it clear who holds what records, where and for how long, and this should include both hard-copy and electronic records.

Where multi-centre research is occurring there will need to be a designated Principal Investigator to oversee the trial activity at the research site and to ensure that the protocol is followed locally in line with ethics, regulatory approval and local procedures.

7.2 The requirements of NHS organisations and Principal Investigators as host sites

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 (including any electronic records/files).

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. Many of the above responsibilities will be delegated to the Principal Investigator

It is the responsibility of the Principal Investigator to manage the day-to-day oversight of the trial at their site and to link in with their R&D Office and the trial Chief Investigator for reporting and operational oversight.

It is important that these roles are clearly documented in practice and procedure, and evident in the trial records, as it is these that will form the basis of the inspection.

8. Pre-inspection activities for inspections

The MHRA will issue a letter of notification 2-3 months in advance. The organisation is expected to produce, within 30 calendar days, a 'Pre-inspection Dossier' that will contain a request for information to help the Inspector:

- 1) understand how the organisation co-ordinates and controls the conduct of the trials it is responsible for; and
- 2) determine how much time should be spent at the site(s) for inspection.

This information includes (but may not be limited to):

Note: The current dossier request is available in electronic form on the MHRA website:

www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Theinspectionprocess/index.htm

- Organisation details
- Contact name to manage logistics
- Organisation charts relating to clinical trial activities
- List of clinical trial processes
- Summary overview of adverse event reporting systems & procedures
- List of computer systems and validation status
- Overview of joint sponsorship or close collaborations
- Overview of all your organisation's facilities in the UK, which are involved in clinical trial activities
- List of clinical trials of medicinal products
- Summary information of clinical trial systems (no longer than 1 side of A4 paper for each of the following):
 - Contract and Agreement Preparation
 - Quality System (including training)
 - Clinical Quality Assurance
 - Project Management
 - Clinical Trial Monitoring
 - Pharmacovigilance
 - Regulatory Affairs
 - Computer Systems
 - Investigational Medicinal Products
 - Data Management & Statistics
 - Clinical Trial Reporting
 - Trial Master File
 - Archiving
 - Clinical Facilities
 - Laboratories
 - Equipment Maintenance

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, these usually relate to specific studies such as recruitment rates, event rates etc, but also may include

specific SOPs. If you have any questions or concerns when you are compiling your dossier these can be discussed by calling any of the MHRA offices where you will be put in contact with an inspector or administrator that can help with your questions.

8.1 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
- Report writing
- Archives
- Investigational sites

How many of these activities are selected will depend upon the main areas of work carried out by the organisation, how much time is allocated to the inspection, and how many studies are selected for the inspection. Where time is limited, or where the inspection is triggered, only critical areas (either to the specific studies selected, or the specific 'referral' questions) will be examined.

9. Inspection Plan

A confirmation letter will be issued once you have been notified of the inspection dates, and this will include details on the logistics of the inspection, and who the members of the inspection team will be.

A number of clinical trials will be selected for inspection though this can change during the inspection visit with the inspectors looking at hosted studies. An outline plan will usually be provided in advance of the inspection dates provided that you meet the timelines for dossier submission. This will allow enough time for clinicians to rearrange clinics so as to work around the statutory inspection commitments. You will be asked to indicate which personnel will be present for interview for each of the activities to be covered. You will need to ensure that interviewees are available at their allocated time.

If someone is unavailable, you may suggest alternative times or locations, just give your reasons. Inspectors reserve the right to deviate from the inspection plan if the results of the inspection warrant this. Furthermore, if something happens during the inspection which means you need to request a change to the inspection plan, don't be afraid to raise this with the Inspection team – it happens more often than you might think! So if you need to leave early because of a sick child, or something else has come up at home, the inspectors will understand, they are human and will accommodate any such requirements.

9.1 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

It is natural to feel nervous during an inspection; if any staff involved in the interview sessions feel that they did not fully explain themselves or wish to add to or correct anything they have spoken with the inspectors about, or if they don't think the inspector has understood, or there is a document that would explain things but the inspector hasn't specifically asked for it. If you speak with the lead inspector time for this can usually be accommodated to ensure the inspector fully understands how trials are managed within the organisation.

9.2 Types of findings

The MHRA currently uses the following criteria to classify inspection findings:

- Critical;
- Major; or
- Other.

The definitions of the findings will be provided in the inspection report, and are available on the website:

www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/Theinspectionprocess/index.htm#5

In general Critical findings are 'show stoppers', that is ones which have a definite (or very near potential to) impact on the safety of the subjects, their rights, or the results of the studies. They are likely to be related to large system failures (or even an absence of a system), in which too much variability in the quality is evident within or between studies.

Critical findings may not warrant MHRA stopping the study, but will give funders, Sponsors and Investigators serious issues to consider, and there is an expectation that action is taken immediately (or at the very least 'quickly') to secure compliance in the specified area.

MHRA have a special process for dealing with Critical findings, and this is covered later.

Major findings, are generally those which have not yet become Critical, but without prompt, planned corrective action, may develop into such an issue – they may be apparent from a lot of failings each not in themselves major, but cumulatively show the system is not operating as intended, and is potentially out of control.

Other findings, are those things not in the above categories but which are identified during the normal inspection and review processes.

Inspectors will during the inspection, make far more comments and notes than appear in the final inspection report, and it can be helpful during the planning and logistics part of the inspection to work out how these will be captured within and between teams to make best use of the inspection process when moving forward, after the inspection. This can usually be achieved by having a scribe present during the discussions/interviews scheduled for the inspection.

A 'Critical' finding is defined as one where:

- a) Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that
 - i) the safety or well-being of trial subjects either have been or have significant potential to be jeopardised, and/or

- ii) the clinical trial data are unreliable and/or
- iii) there are a number of Major non-compliances (defined in (c) and (d)) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (c) and (d))

A 'Major' finding is defined as:

c) A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

d) Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have occurred within a single area of responsibility, indicating a systematic quality assurance failure.

An 'Other' finding is:

e) Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

The implications are:

- Critical findings are routinely referred to the MHRA's Clinical Trial Inspection Action Group (CTIAG). These 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 through provision of a corrective and preventative action plan.
- 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.

9.3 Post-inspection MHRA report to the organisation

A report is issued within 25 working days of the end of inspection. The MHRA will expect responses to be received within 25 working 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.

If you receive a report that doesn't quite make sense, or doesn't reflect your understanding of what was said at the time, it is worth contacting the Inspector who led the inspection (where possible) or another member of the inspection team to get clarification. It is much better to sort out any queries you have before spending your time (and that of others) taking actions and correcting things that have been misunderstood, or writing a corrective action plan and response that can't be achieved.

In the event of a critical finding, the organisation is likely to be asked to respond to the finding within a shorter timeframe than the standard 25 working days; the timeframe will depend on the urgency of the action required, for example the need to safeguard the safety of trial subjects.

9.4 Corrective Action Preventative Action (CAPA) Plan

Organisations are required to respond to the inspection findings, and as part of this it is recommended that organisations devise a Corrective Action Preventative Action Plan.

Organisations should be realistic about the time lines proposed for completion of corrective actions, as these will be used at the time of any re-inspection, and may be referred to if the MHRA receive a referral about your organisation, or question from another Regulatory Authority.

The GCP inspector will review responses and provide feedback to the organisation regarding any finding responses that are not adequate (for example if they don't answer the question asked, or don't provide enough information), or about which the Inspector would like further information.

Inspectors also review the CAPA to see if what is proposed is feasible to achieve given the resource, so try not to be over ambitious – be realistic (permitting some 'give' in the plans for real life) – they are looking to see what priorities you have established and who is taking responsibility within the organisation to ensure the actions are completed. The most successfully implemented CAPAs are managed by the operational teams and have management buy-in at the Divisional level, but the results of which are shared organisation wide to prevent 're-inventing the wheel' syndrome. It can be useful to consider at the planning stage how actions will be taken forward.

The organisation is given ONE opportunity to provide clarification of responses and additional information. Inadequate responses will be documented in the post-inspection summary and should these responses be to major findings, this may cause early re-inspection. If there are inadequate responses to critical findings, these will be dealt with by the Inspection Action Group to agree a revised action plan with the organisation.

The organisation will be assessed at the next inspection in terms of whether the corrective and preventative actions have been implemented – has the organisation done what they said they would? If previous major findings have not been addressed then a critical finding may be given.

10. 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 awareness
- Project review
- System development

10.1 Organisational Awareness

Perhaps the most difficult task facing the R&D Manager is to 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 possible to predict the likelihood of an inspection as a result of completion of the GCP compliance report. 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. Inspection will be based on the GCP Compliance report submitted by the organisation.

The following list suggests some methods you may use to communicate the importance of MHRA Inspection:

- The possibility of an MHRA inspection could be placed on the organisation's risk register as this will help to ensure that resources can be allocated to help with managing the inspection;
- Involve the risk management processes already in place in the organisation
- Ensure the Chief Executive and/or Medical Director and/or Director of Research write to all researchers involved in clinical trials explaining the importance of an inspection. It is also useful to invite the above management to attend the Opening and/or Closing meeting of the inspection;
- 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 and/or consider a part of the R&D website where updates and information can be posted relating to inspections

It is a really good idea to tell everyone when a dossier request is received. It is important not to 'scare' staff however as this can lead to them being unnecessarily nervous during the inspection.

10.2 Project review

Prepare your CTIMP project list

The first thing the MHRA will do prior to 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.

Non-commercial organisations will have a database or spreadsheet containing information on their research activity. All CTIMPS should be 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.
- 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

Organisations would be well advised to record information on CTIMPS in line with the requirements of the inspectorate, irrespective of whether you are due an inspection. You should refer to the excel spreadsheet provided by the MHRA which contains all relevant data points.

10.3 Review of Trial Files

As detailed in section 8 of the "Guidelines for GCP –E6", every research study must have the following sets of essential documents in:

- 1) Sponsor's File (usually held by R&D or sponsor)
- 2) Trial Master File (usually located in the CI's Research Team Office)
- 3) Site File

- Ensure that trial files are up to date and contain all the necessary documentations.
- If any information is missing, locate it where possible, or create a file note stating where the document is, or why is not present
- Ensure that all files for studies that are ended are archived appropriately

For multicentre studies, the Sponsor's TMF will include all essential documents from all sites except those documents containing participant's identifiable information.

It is routine for NHS or HEI to have folders containing the organisation's governance approval documents on each study located in the organisation's central research office. Invariably, copies of most of the documents in the folder should also be located in the Sponsor's TMF described above. This folder is often called the **R&D Folder** but may be known by other names in various organisations. As a sponsor, the Inspector may also request for a copy of the R&D Folder for the study to verify the Sponsor's approval system.

Many non-commercial organisations use modified versions of Section 8 of the ICH GCP guidelines as a basis for their file requirements; the rational for reduction or replacement of the documents kept should be documented either by study, policy or procedure.

10.4 System development

Process management and SOPs need to be in place to ensure that the systems for conducting CTIMPs are robust.

Education and training such as GCP training and update, and training in SOPs needs to be put in place. There is no statutory time line for when update training should be undertaken. The extent and frequency of training is an organisation decision. However once you have decided on the frequency this should be written into your SOP. You need to ensure that are able to deliver to the timelines stated. Remember that you need to be able to put out updates to changes in legislation in between times, and this can be by newsletter or email or other such internal media, just be sure that those conducting CTIMPs are in receipt of these updates.

Be aware that the presence of a GCP certificate does not always demonstrate an awareness of GCP at the operational level, and Inspectors will be looking at documentation, procedures, practice, and in discussions to see that GCP and the requirements of the legislation have been implemented. It is important that the implementation should not be so bureaucratic as to be prohibitive to good research, and has, on some inspections been seen to be counter intuitive to GCP in that the SOP has directed practice which compromises the rights and safety of the subjects and/or the data.

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

- Contract Management
- Document Management
- SOP and Report Writing
- Project Management
- IMP Management
- Archives
- Monitoring
- Regulatory Submissions
- Laboratories
- Pharmacovigilance
- Quality Assurance
- Trial master file
- Data-management
- Training – GCP, SOPs and Consent
- Statistical Management
- Computer Systems
- Equipment Maintenance
- Delegation of Responsibilities

11. MHRA Inspection – Practical Advice and Logistical Arrangements

11.1 Preparing staff

- The final inspection plan should be circulated as soon as possible to all identified staff
- Staff should be clearly briefed and you should ensure they are up to date with their knowledge of relevant policies and procedures
- Staff training records should be up to date
- Obtain medical notes as required by inspectors. As these may not be requested in advance liaise with medical records to ensure there is a process for obtaining notes as needed during the inspection
- You may wish to provide your staff with the list of possible questions the inspectors might pose by way of preparation (speaking with other organisations previously inspected may help with this)
- You may also wish to conduct mock interviews

It is strongly recommended that this process is used to help staff prepare themselves for a reasonable discussion about what they do, how, when and why. They may also be asked about who else is involved and how things work between parties (so that the process is seamless). There are no trick questions, the interview sessions are in place to assist the inspectors in understanding the processes followed for running clinical trials within your organisation.

There are certain things it helps for staff to know

- It is normal to be a bit nervous – inspectors are aware of this and will always try to put staff at ease
- If you know your study well, you know it better than the inspector, so be prepared to spend time providing explanations for things you think may be obvious
- The inspector is trying to understand what you do, how you do it and how that fits with everything else they have been told on inspection. Last week they were doing the same somewhere else, so it may need explaining more than once, and in more than one way.

Discussions are not intended to catch people out, but may be very directed to specific questions, particularly where documentation has been reviewed in advance of the allocated 'interview' slot.

For triggered inspections, they will be directed to matters of concern, but may also be directed to the surrounding system aspects to gain perspective and context.

In all cases, if someone wants to have a second person present, this is generally expected, permitted and acceptable, but it is good to raise with the Inspector at the earliest opportunity.

In some circumstances, where the discussions don't go to plan, a discussion may be re-scheduled, or someone may be asked to come back, if other things come-up during inspection – this too is a normal part of the inspection process, and nothing for staff to be worried about. Furthermore if staff have limited time due to other commitments, this should be raised so that timings and arrangements etc can be respected by both parties.

11.2 Logistical Issues to Consider for the inspection:

- Book meeting rooms in advance for opening and close out meeting, and try to keep one room available for the duration of the inspection for the Inspector's interviews and document review sessions.
- The document review room should preferably be one that can be locked during the course of the day if the Inspector's are out, this also saves moving confidential information when the room is unoccupied. It is also useful to have a bin in this room.
- Order lunch and adequate refreshments during the day for the Inspectors if possible. This enables them to 'work through' facilitating their review of the documentation provided for the inspection (this is not in any way a requirement however and if this is not possible it is not a problem).

- Ensure you have scribes available for the interviews, particularly if there are parallel sessions taking place.
- Advise your R&D team that they cannot take leave that week and they should expect to be in early, and possibly be a bit late in the evening.
- The R&D manager, who is more than likely the person to lead the inspection on behalf of the Trust will need people to support and locate documents as required.
- Obtain mobile contact numbers for members of the research teams.
- Arrange briefing and debriefing of teams at the end of each day as required.
- Do not underestimate the resource implications during pre-inspection, inspection, and post-inspection periods.
- Have a trolley available to move files and patient notes around.
- Teams will need supporting during this process.
- Consider ongoing communication with your research team – for example you may chose to bring staff together at the end of each day and liaise with staff to be interviewed the next day, or send a 'round robin' update via e-mail.
- Instant message communicators, pagers and mobiles are also good ways of keeping the next person in the queue updated.

11.4 Stage 3: Inspection visit

An example of a full inspection plan is shown in Appendix F. Some points to note at the visit:

- The inspector will begin with an opening meeting outlining the scope and purpose of the inspection. MHRA inspectors have warrant cards, which they are happy to produce to identify themselves at the beginning of the inspection.
- The inspection is typically conducted by 2-3 inspectors over 3-4 days for an initial inspection; the time and/or number of inspectors may be reduced for a re-inspection.
- The inspectors may deviate from the initial list of clinical trials if they need to see further examples.
- The inspectors will conduct interviews with staff and review documents looking for evidence to back up information provided in interviews.
- Additional requests for documentation will be made, which you will be expected to provide as soon as possible during the inspection to enable the inspectors to review. These are tracked on a document request form – it is useful for you to photocopy this form at regular intervals to keep track of what has been provided and what is still outstanding. Some organisations copy all requested documents rather than providing originals – this is very resource intensive. Most documents are used for reference only during the inspection therefore to save time provision of originals is fine (although let the inspectors know they are originals so no notes are written on them!). Any documents that the inspector wishes to retain will be clearly identified, in which case provision of a photocopy is usually acceptable.
- All interviews should be documented for reference purposes after the inspection.
- A nominated person should escort the inspector to all sessions on the inspection plan.
- Staff should be aware that the exact timings of the inspection plan may be deviated from, and as such you need to consider how time-keeping will be managed to prevent your staff or the Inspectors 'hanging around' for one another.

11.5 Stage 4: Post-inspection

The inspectors will provide verbal feedback of their findings at the end of the inspection visit. Attendance at the feedback sessions is at the discretion of the organisation, you can be as inclusive or exclusive as you wish. You should take notes of what is said at this session to ensure it reflects the final written report.

It should be noted that the factual matter contained in the Inspection Report relates only to those things that the inspection team sees and hears during the inspection process. Once adequate responses have been received from the organisation, a closing letter and GCP Inspection Statement is issued, which includes details of the findings from the inspection. This is not a certificate of GCP compliance, but simply a statement to say that the inspection was performed and what the issues were. The

outcome of your inspection will be taken into consideration and in part determine the frequency and scope of subsequent inspections as part of the risk based inspection programme.

12. Some suggested Dos and Don'ts

Do	Don't
• Be completely open and honest at all times. • Audit studies chosen for inspection prior to the inspection – but remember to look at content as well as 'presence' of documents. • Acknowledge and document areas that you know need development. • Implement a thorough communication strategy. • Provide information on relevant policies and procedures including GCP requirements to staff involved in the inspection in advance.	• Do not make Major changes to policies and procedures in the weeks leading up to the inspection. • Do not write and implement Standard Operating Procedures that are overly complex and above the required standards. You will be inspected on your SOPs as well as the regulatory requirements. Failing to meet your SOPs will result in inspection findings even if you are meeting the regulatory requirements. Where possible use 'guidance' instead of rigid SOPs.

12.1 General comments

- Organisation-wide inspections can highlight 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 may require the R&D staff to work closely with previously unmet colleagues and assist with developing excellent working relationships for the future.
- The inspection may help provide leverage to secure resources for and implement necessary changes to systems and policies.
- The vast majority of inspection findings relate 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.

12.2 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

13. Common findings from inspections conducted by the MHRA

This information is a collation of findings from the MHRA and non commercial organisations that have been inspected.

Organisation oversight of clinical trials

- Over delegation of responsibilities to CI/PI without ensuring appropriate training/expertise in delegated areas
- Lack of systems to appropriate identify trials that fall under the legislation
- Poorly documented/incorrect sponsorship/Legal Representative arrangements
- Lack of R&D approval
- Failure of R&D systems to ensure awareness of all clinical trials
- Approval & oversight of subcontractors
- Failure to obtain MHRA and REC approvals at all, and also for substantial amendments, including one trial conducted that had received a grounds for non-acceptance letter from the MHRA.
- Failure to address remarks/conditions on the CTA issued by MHRA
- Failure to issue End of Trial notifications.
- Little or no oversight of pharmacovigilance requirements when delegated to the principal investigator
- Ensuring staff were trained in GCP/Legislation
- Failure to report serious breaches of trial protocol/GCP to MHRA.
- Lack of oversight and control when undertaking role of co-sponsor
- No document control
- Unclear sponsorship arrangements for co-sponsored trials and for DDX studies rolled over to CTA studies
- No system for informing researchers of updates to policies, training, systems and legislation
- Not including Non commercial hosted trials in organisation oversight procedures
- Failure to comply with protocol/GCP compliance
- Failure to report serious breaches

Pharmacovigilance

- Inadequate pharmacovigilance systems and/or inadequate use of systems in place
- Lack of involvement of Principal or Chief Investigator
- Lack of awareness of, and compliance with, 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
- Failure to notify R&D/Sponsor of SAEs/SUSARs
- Failure to comply with legislative requirements
- Lack of/ineffective systems to comply with part 5 of the legislation
- Failure to report SUSARS
- Incorrect/outdated reference document for expectedness assessment
- Failure to submit Annual Safety Reports
- Robust documentation, data basing and follow up of SAEs
- Inadequate safety reporting
- Failed response from emergency / out of office telephone numbers when tested

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
- Evidence that formal procedure/systems were not in place or were weak:
- Regulatory Green Light, in particular for multicentre trials, but own trials also affected.
- Lack of/inadequate QP Certification.
- Importation and Manufacturing IMP without the appropriate Licence from Competent Authority
- Systems to ensure pharmacy involvement/knowledge of trials being undertaken to ensure legislation met, input into CTA submission and review/receipt of protocol amendments to ensure accurate information about IMP is supplied to MHRA/REC.
- Use of expired/recalled/non GMP manufactured IMP
- Poor/ineffective blinding system
- Poor accountability of IMP
- Lack of agreements with IMP suppliers
- Uncontrolled site to site transfer

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 CI awareness and without agreements or robust systems in place

Indemnity

- Conflicts in contracts leading to more than one party providing indemnity or neither part providing indemnity

Quality systems

- Lack of essential SOPs
- Uncontrolled documents used in place of SOPs
- Insufficient review of SOPs / Protocol to ensure adequate reflection of 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
- Version control logs
- Failure to adequately document trial activities
- Insufficient and poor data recording
- Failure to retain essential documents

Informed consent

- No records of consent being taken
- Missing elements
- Inconsistencies with protocol
- Forms not updated with amendments, poor version control, not signed or completed correctly
- Incorrect form used

- Unclear process
- Lack of consistency with where original consent forms are kept (should be addressed in SOP)
- Letter to be sent to MHRA after first patient consented
- Lack of involvement of CI/PI
- Documents used to support process not ethically approved
- Breaches of subject confidentiality - the subject was identifiable from documentation transferred between organisations without explicit subject consent.

Ethical approval

- Lack of approval for study advertising
- Study conduct at sites outside of those in the application
- Trial file does not contain information on the ethics committee constitution
- Conducting a trial without necessary CTA/REC approvals

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
- Over delegation of responsibilities from PI to research staff

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

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
- Lack of documentation of validation of computer systems

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

Sample & Laboratory Management

- Unidentified or unexpected laboratory samples analysed for a range of tests - this may be outside the protocol and therefore without consent
- Calibration records for equipment used in study
- How do laboratory results get back to researcher

- PI keeping an eye on laboratory ranges and PI sign off on results

Publication

- No formal policy to assure the appropriate, timely publication of research findings (N.B. both positive and negative research findings should be published i.e. put in the public domain)

Peer Review

- Lack of defined process
- Need to ensure that peer review documentation references protocol version and date

Pharmacy

- Use of template prescriptions rather than NHS prescriptions
- Incomplete drug accountability records
- Ensuring pharmacy are aware of protocol amendments
- Identification of IMP versus non IMP studies
- How do pharmacy know which brand of drug

Appendix A: Key definitions

Advanced Therapy Medicinal Product An advanced therapy medicinal product is a medicinal product which is prepared industrially by a method involving an industrial process. ATMPs fall into three categories:

- Gene Therapies
- Somatic Cell Therapies
- Tissue Engineered Products

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

Appendix B: Useful Web Pages

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 May 2011

The Medicines for Human Use (Clinical Trials) Regulations 2004

www.legislation.hmso.gov.uk/si/si2004/20041031.htm, accessed May 2011

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

<http://www.opsi.gov.uk/si/si2006/20061928.htm>, accessed May 2011

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, accessed May 2011

Medicines and Healthcare products Regulatory Agency (MHRA) Homepage

<http://www.mhra.gov.uk>, accessed May 2011

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
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (MP)? ⁱ	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to <u>any</u> of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	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. If you answer yes to <u>any</u> of the questions below go to column D.	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. If you answer yes to <u>any</u> of the questions below go to column E.	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 & 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.
A.1 Is it a substanceⁱⁱ or combination of substances presented as having properties for treating or preventing disease in human beings? 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? A.3 Is it an active substance in a pharmaceutical form?	B.1 Are you <u>only</u> administering any of the following substances? - Human whole bloodⁱⁱⁱ; - Human blood cells; - Human plasma; - Tissues except a somatic cell therapy medicinal product^{iv}; - A food product^v (including dietary supplements) not presented as a medicine; - A cosmetic product^{vi} - A medical device	C.1 To discover or verify/compare its clinical effects? C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3 To identify or verify/compare its adverse reactions? C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1 To ascertain or verify/compare the efficacy^{vii} of the medicine? D.2 To ascertain or verify/compare the safety of the medicine?	E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned? E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation? 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^{viii}? E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? 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? E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

ⁱ 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.

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

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

^{iv} 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.

^v 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.

^{vi} 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.

^{vii} 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.

^{viii} Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/IsaclinicaltrialauthorisationCTArequired/index.htm#1>
(accessed May 2011)

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: • Protocol/amendment(s) and • CRF • Informed consent form • Patient/Parent Information Sheets	X	X
8.3.3	Dated, documented approval of independent ethical committee of the following: • Protocol amendment(s) • Revisions of: Informed consent form- Patient/Parent Information Sheets • Any Other documents where approval required.	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

Appendix E: Examples of MHRA inspection plans

Example 1

Day One	Proposed start time 8:30	Personnel to be interviewed
Opening Meeting (I1) Introduction to Inspectors and over-view of inspection plan and procedures.	8:30 – 9.00	Open session with the Inspectors for brief introduction to inspection process.
Research & Effectiveness Department (I1) 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.	9.00 – 11.30	Over-view of how the Organisation controls trials: R&D Information Officer. R&D Manager (Governance and Quality). General clinical trial/GCP training: RDSU Co-ordinator. R&D Manager (Governance and Quality). Investigational Medicinal Products: Quality Assurance Manager, Pharmacy. Director of Pharmacy
Archiving of (Clinical Trial) Patient Records (I2) Visit to Medical Records Department – plus visit to supplementary areas for children's and surgery records (time permitting).	11:30 – 12:30	Medical Records: Assistant Health Records Manager Children's –Patient Services Manager Surgery –Medical Records Supervisor
Lunch and Document Review	12.30 – 13.15	

Day One	Proposed start time 8:30	Personnel to be interviewed
Pharmacy Facilities (I1) 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) Chief Pharmacist, BCH Pharmacy
Information Technology (I2) 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.
Document Review 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. The times and activities listed above are provisional and may be adjusted during the inspection.		

Day Two		Proposed start time 8:30	Personnel to be interviewed	
Facility Tour and Investigator Meeting (I2) To be included in the session: 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. Meeting with the Principal Investigator (est 30 – 45 min) Meeting with designated research staff Review of trial-specific records and diary/appointment information. 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	
Lunch and Document Review		12.00 – 13.00		
PLEASE NOTE PARALLEL SESSIONS				
Facility Tour and Investigator Meeting (I2) Session requirements as per previous	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
Inspectors Review Meeting 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. The times and activities listed above are provisional and may be adjusted during the inspection.				

Day Three	Proposed start time 8:30	Personnel to be interviewed
Tour of Laboratories Brief visit to areas which perform clinical trial sample analysis (Haematology, Clinical Chemistry, Microbiology) 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
Tour of Radiology/Imaging Specialists (Outside the Oncology CTU) Visit to clinical trial supporting areas involved in key safety and efficacy variables.	10.00 – 11.00	Professor of Radiology. Superintendent radiographer (CT)
Outstanding Issues Resolution of outstanding items	11:00 – 12:00	As appropriate from inspection proceedings (to be highlighted at previous sessions.)
Lunch and Document Review	12.00 – 14.00	
Closing Meeting (I1) 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. The times and activities listed above are provisional and may be adjusted during the inspection.		

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.	11:15am – 12:15am	Pharmacy Staff
Review facilities, procedures and records in main pharmacy and in Sterile Unit.		
Check on drug accountability for chosen trials.		
Lunch	12:15 – 1:15	
R&D Office	1:15 – 3:00 RVI	Research Governance Manager and Head of R&D
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		
Break and travel	3:00-3:30	
Pharmacy – Oncology	3:45 – 5pm Newcastle General	Cytotoxic preparation staff
DAY 2		
INSPECT FACILITIES AND RECORDS OF 1 st CHOSEN TRIAL.	About 3.5 hours	Trials staff
INTERVIEW STAFF INVOLVED WITH TRIAL.		
Two inspectors move to 2nd & 3rd Trials at 10:45am.		
INSPECT FACILITIES AND RECORDS OF 2 nd & 3 rd CHOSEN TRIALS.	About 3. 5 hours	Trials Staff
INTERVIEW STAFF INVOLVED WITH TRIAL.		
Give feedback to investigator (could be done in closing meeting on 4th day)		
DAY 3		
Option to return to resolve outstanding issues in trials inspected on day 2.	(morning)	
IT demonstration (RVI)		
University issues/perspective (RVI)	9 – 11 am	IT Manager
Pathology (RVI)		
(Clin. Chem and haematology).	11- 12noon	Assistant Registrar
Imaging Dept. (NGH)		
	12 – 1pm	
	Travel	Laboratory staff
	1:15 – 2:30pm to include lunch	
		Imaging Staff
Further trial related issues	3 – 5pm	Relevant staff
DAY 4		
Closing meeting	11am	Attendance to be as organisation require