

Title: MHRA Inspection	
Effective Date: 19/11/2019	Review Date: 19/11/2021
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Approver: University Research Ethics Committee	

1. Scope

1.1 This Standard Operating Procedure (SOP) applies to Clinical Trials of Investigational Medicinal Products (CTIMPs) that fall under the Medicines for Human Use (Clinical Trials) Regulations 2004 and that are sponsored or co-sponsored by Bournemouth University (BU).

The aims of the MHRA are threefold:

- 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.

1.2 This SOP applies to all research team members delegated to work on CTIMPs or medical device trials sponsored or co-sponsored by BU.

2. Responsibilities

The *Sponsor* and *Clinical Governance Advisor (CGA)* are responsible for supporting researchers in preparing and participating in MHRA inspections.

The *Chief Investigator* is responsible for ensuring that study documentation is accurate, up to date and ready for inspection at all times. They are also tasked with providing the Sponsor with the necessary documentation in order for them to prepare an inspection dossier, or to provide the MHRA Inspectors with documents upon request.

3. Procedure

Medicines and Healthcare products Regulatory Agency (MHRA) – types of inspection

3.1 The MHRA conduct three types of Good Clinical Practice (GCP) inspections:

- The routine inspection;
- The requested inspection;
- The triggered inspection.

3.1.1 The majority of inspections are routine in nature and carried out as part of the national statutory inspection programme. **Routine inspections** are an open process with open communication between the lead Inspector and the organisation being inspected.

3.1.2 A **triggered inspection** will be prompted by information received such as data credibility and/or patient safety issues and may be study-specific or system-based. The lead investigator will discuss and inform the organisation as to the process and procedures to be followed during the visit, as these are decided on a case-by-case basis.

3.1.3 **Requested inspections** are prompted by regulatory applications (MHRA and European Medicines Agency [EMA] coordinated applications) to ensure that trials are being conducted in accordance with Good Clinical Practice (GCP) regulations.

3.2 The MHRA also carry out **Sponsor inspections** on those organisations named as Sponsor, or that are co-sponsoring a CTIMP. The Sponsor must ensure that the study meets the relevant standards, and that ongoing arrangements are in place for the management, monitoring and reporting of the trial. When the MHRA carries out these types of inspections, they may also carry out a visit at one of the sites hosting the trial. The MHRA will usually give approximately six weeks' notice prior to the inspection, with the timeline for the report starting after the last day of the final site inspection.

3.3 The **Investigator site inspection** can occur at any host site (with an external Sponsor) where the MHRA wishes to inspect the conduct of the trial by the investigator, and likewise the role of the Sponsor in overseeing the trial. NHS organisations inspected will be scrutinised as to whether they are 'fit for purpose', by inspection of facilities such as Pharmacy, laboratories etc.

UK Clinical Trials Regulations

3.4 The UK Clinical Trials Regulations set out conditions and principals for Good Clinical Practice for CTIMPs. The below are taken from the updated Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 –

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.

Prior to the inspection visit

3.5 The MHRA will expect to see procedures in place at NHS organisation ensuring that the trial is conducted in accordance with GCP and Clinical Trials Regulations, for example ensuring that there are adequate staff training records, quality systems are in place in support departments and that the conduct of the trial is in accordance with the protocol.

3.6 The MHRA will notify organisations by letter 2-3 months in advance of an inspection. The Clinical Governance Advisor and Head of Research Development & Support must be made aware of this notification via email, as soon as possible, on receipt. The organisation is then expected to produce, within 30 calendar days, a *Pre-inspection Dossier* which will contain information that will help the Inspector –

- Understand how the organisation co-ordinates and controls the conduct of the trial(s) it is responsible for; and
- Determine how much time should be spent at the site for the inspection.

The current dossier template is available here alongside the Excel spreadsheet on which the organisation's current trials should be identified, and a checklist to help prepare the dossier- <https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials>. The dossier is

[completed by the Sponsor, and as such, the completion and submission of the dossier should be overseen by the Clinical Governance Advisor and Head of Research Development & Support, as Sponsor's representative.](#)

3.7 Once the organisation has been informed of the inspection date, then a confirmation letter will be issued which will detail the logistics of the inspection, and which members of the inspection team will be in attendance. Examples of MHRA inspection plans can be found in the appendix (R&D Forum, 2011).

Preparing for an inspection

3.8 Before the inspection begins, the organisation will be asked for a list of IMP trials being hosted and sponsored, so that the Inspectorate can properly plan the inspection.

3.9 Essential documents pertaining to the trial(s) being inspected should be made available:

- 1) Sponsor's File – this should contain all essential documents from all participating sites, except documents containing participant identifiable data;
- 2) Investigator Site File.

The organisation should ensure that the files are up to date and contain all the necessary documentation. If there is information missing, then efforts must be made to locate it, alternatively a file note may be created stating where the document is, or why it is not present in the file. The Inspector may make additional requests for documents and will expect these as soon as possible during the inspection. In order to supply them with the documents as soon as possible, a 'runner' should be identified prior to the start of the inspection. The runner should be readily available throughout the visit.

3.10 The medical notes of participants on selected studies should be obtained and a plan agreed with medical records to ensure that note can be requested when required, during the inspection.

3.11 The organisation should also ensure that there are up to date training records, SOP records and GCP certificates in place for trial staff.

3.12 The final inspection plan should be sent to all identified staff as soon as possible so they can make sure that their training records, and knowledge of policies and procedures are up to date. Staff should likewise be clearly briefed on the inspection visit and assured that the questions they receive are posed by the Inspector so as to understand the processes followed for running clinical trials within the organisation.

3.13 Make sure there is adequate meetings room space for the inspection and the appropriate facilities available for the Inspectors to conduct their interviews and document reviews.

In the case of routine inspections (and sometimes with triggered inspections), a number of clinical trials will be selected for review, although this number can change during the visit,

with the Inspectors looking at hosted studies. An outline plan will be provided in advance of the inspection visit, allowing clinicians enough time to rearrange clinics, and other appropriate staff at the site, and at BU, to reschedule commitments, in order to work around their statutory inspection commitments. The organisation will also be required to indicate which personnel will be present for interview, for each of the activities to be covered, ensuring that interviewees are available at the time allocated.

3.14 If a staff member is unavailable, then alternative times or locations may be suggested, alongside an explanation. In addition, in the event of personal emergency, the inspection team will be flexible in making changes to the plan.

Lunch is to be provided for the Inspectors, for the duration of the visit.

Ensure that a 'scribe' is available for and present at all the interviews and meetings to take notes of the discussions. Recordings are not permitted.

The inspection visit

3.15 There will be an opening meeting in which the purpose of the inspection will be outlined, alongside instructions and methodology. It is strongly advisable for the appropriate Head(s) of Research and the Deputy Dean for Research & Professional Practice for the Faculty/Faculties which members of the research team come under, to be present at this meeting. The Clinical Governance Advisor, Research Governance Advisor, R&KEO Project Delivery Manager and Head of RDS should make every effort to attend the meeting also. The inspection will be conducted in accordance with a prearranged plan and will include a combination of staff interviews, document review, and facility visits – coordinated by the 'runner'. The MHRA will provide feedback of general findings at a closing meeting, which should be scribed, as mentioned in point 3.14 above. The above staff members should be present at this meeting also.

The initial inspection is typically conducted by 2-3 Inspectors over a 3-4 day period.

Types of findings

3.16 The MHRA uses the following criteria when classifying inspection findings:

- Critical;
- Major;
- Other.

3.16.1 **Critical** findings are generally those that have a definite (or very near potential to) impact on the safety and rights of the participants, and the results of the trial. Critical findings are likely to be related to large system failures, or absence of a system, evidencing too much variability in the quality within or between studies.

The MHRA may not stop a study once a critical finding is identified, however funders, Sponsors and Investigators will be expected to take action immediately to ensure compliance in the area in question. Re-investigation may occur as a result.

3.16.2 **Major** findings are those that have not yet become critical, but without prompt action, have the potential to develop into such an issue. It may be that there are a number of failings

that are not major, but together show that a system is failing and not functioning adequately. These findings are addressed through provision of a corrective and preventative action (CAPA) plan.

3.16.3 **Other** findings are items that do not fall within the above categories, but that are highlighted during the inspection and review.

Post-inspection procedure

3.17 The Inspectors will give verbal feedback of their findings at the end of the inspection visit, and it is recommended that notes are taken in order to ensure what is written in the final report is accurate. A report is issued within 25 working days of the end of the inspection and the MHRA will expect responses to be received within 25 working days of despatch. The organisation may request clarifications and ask questions if required. The MHRA will issue a summary letter and an inspection certificate.

In the event of a critical finding being identified, the organisation is likely to be asked to respond within a shorter timeframe than the standard 25 working days, depending on the urgency of the action required, the timeframe will be stipulated: for example, the urgent requirement to protect the right and well-being of trial participants.

Corrective Action Preventative Action (CAPA) Plan

3.18 Organisations must respond to inspection findings and are recommended to do so via a CAPA plan (which the MHRA will likewise review). The CAPA should be discussed with the CI and research team as appropriate. In proposing timelines for completion of corrective actions, organisations should be realistic, as these will be used at the time of re-inspection and referred to should the MHRA receive a referral about the organisation, or question from another Regulatory Authority.

The CAPA will be overseen by Research Development & Support and held centrally within the department. The CAPA will feed into the Clinical Governance Group which meets quarterly, and the University Research Ethics Committee that meets every 3 months. Compliance with the CAPA will be overseen by Research Development & Support.

3.19 Should the Inspector be dissatisfied with any responses received, they will provide feedback to the organisation. Organisations have only one opportunity to provide their responses in clarifying any queries from the Inspector, so if they receive inadequate responses, this will be documented in the post-inspection summary. Should these be in response to major findings, this may cause early re-inspection. If in response to critical findings, then the Inspection Action Group will agree a revised action plan with the organisation.

3.20 At the next inspection, the Inspector will assess whether the corrective and preventative actions from the CAPA plan, have been implemented. Should previous major findings still be outstanding, then a critical finding could be given.

Common findings from MHRA inspections

Found below is only a small selection of common findings arising from MHRA inspections of non-commercial organisations:

- Over delegation of responsibilities to CI/PI without appropriate training/expertise;
- Lack of R&D approval;
- Failure to obtain MHRA and REC approvals, failure to obtain such approvals for substantial amendments;
- Lack of training in GCP/Legislation;
- Failure to report serious breaches of trial protocol/GCP to the MHRA;
- No document control'
- No system for informing researchers of updates to policies, training, systems and legislation;
- Failure to comply with protocol/GCP guidelines;
- Lack of involvement of CI/PI;
- Failure to identify and report Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs);
- Failure to submit Annual Safety Reports;
- Lack of signed documentation pertaining to the IMP (e.g. shipping records, drug accountability);
- Insufficient records for the chain of custody for marketed products used in clinical trials;
- Poor blinding system;
- Use of expired IMP;
- Poor contract management (e.g. lack of consistency between protocol and contract);
- Insufficient review of SOPs;
- Lack of documentation surrounding trial activities;
- Poor data recording;
- Lack of involvement of CI/PI in informed consent process;
- Non-ethically approved documents used during informed consent process;
- Breaches of subject confidentiality;
- Lack of GCP certification amongst PIs and trial staff;
- Incomplete delegation logs;
- Lack of documented PI involvement in the trial and over-delegation of duties by PI to trial staff;
- Unsecure storage of participant records;
- Lack of documentation showing validation of computer systems;
- Data management procedures and systems found to be inadequate;
- Non-protocol samples taken and analysed by laboratory;
- No formal policy to assure the appropriate and timely publication of research findings;
- Lack of defined process surrounding peer review;
- Incomplete drug accountability records;
- Pharmacy involvement in protocol amendments.

4. Abbreviations and definitions

CAPA	Corrective Action Preventative Action (plan)
CGA	Clinical Governance Advisor
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
EMA	European Medicines Agency
GCP	Good Clinical Practice
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research & Development (NHS Research Governance)
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

5. Related documentation and references

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. (2011). Research and Development Forum

Appendix

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 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 (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	
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 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 s 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 Nurse
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 appropriate) should be made available for the personnel interviewed and may be requested for Other personnel. The times and activities listed above are approximate 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
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 (CTU)
Outstanding Issues Resolution of outstanding items		11:00 – 12:00	As appropriate from inspection points 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 appropriate) should be made available for the personnel interviewed and may be requested for Other personnel. The times and activities listed above are approximate and may be adjusted during the inspection.			