Preparing for a Good Clinical Practice (GCP) Inspection

NJRO-GEN-SOP-023

Contents

1. Background/Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) Good Clinical Practice (GCP) Inspectorate assesses the compliance of organisations with the UK and EU legislation relating to the conduct of clinical trials in Investigational Medicinal Products (IMPs). This is achieved through carrying out inspections of sponsor organisations that hold clinical trial authorisations or organisations that provide services to clinical trial sponsors, such as contract research organisations (CROs), NHS trusts and clinical laboratories.

Three types of inspections may be conducted under the statutory programme: routine national inspections; triggered national inspections and requested inspections. The majority of inspections are routine inspections, carried out as part of the national risk-based statutory inspection programme. These can either be systems based or trial specific.

GCP systems inspections examine the systems used by an organisation to conduct clinical trials. In this instance, inspectors will select a number of clinical trials to examine how the organisation's trial procedures are applied. One or two investigator sites involved in the selected trials may also be inspected.

Trial specific GCP inspections assess clinical trials that have been completed and reported.

2. Purpose

The purpose of this SOP is to describe the procedure for facilitating the MHRA's GCP inspection process, including inspection planning, conduct and reporting. It also explains the process of closing out an inspection and how any serious findings should be actioned.

3. Scope of Document

This SOP applies to all Newcastle Joint Research Office (NJRO) staff, research delivery staff, Chief Investigators (CIs) and Principal Investigators (PIs) within the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH) who are involved in both NuTH sponsored and hosted Clinical Trials of Investigational Medicinal Products (CTIMPs), Advanced Therapy Medicinal Products (ATMPs) and Clinical Investigations of non-CE marked devices which may be subject to inspection by the MHRA.

This SOP also applies to trial management teams who have been delegated the responsibility of overseeing clinical trials on behalf of NuTH as sponsor.

Although the MHRA is the Competent Authority in the UK, other regulatory authorities may select a UK site for inspection. If teams receive notification of inspection (by the MHRA or

other regulatory body), this should be notified to the NJRO via email to: nuth.genericqueries@nhs.net and tnu-tr.sponsormanagement@nhs.net.

The MHRA also conducts GCP inspections of laboratories which analyse human samples collected in support of endpoint data, or where the analysis is critical to the conduct of the trial. As such, this SOP also applies to laboratory staff involved in processing/analysing research samples.

4. Definitions

4.1 Inspection: The act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority to be related to the clinical trial.

4.2 Routine Inspection: Scheduled inspections that organisations undergo on a periodic basis. Organisations are notified of routine inspections in advance and these inspections are generally systems based, whereby inspectors examine systems and procedures used by the organisation to conduct clinical research in order to comply with GCP requirements. These inspections can also be trial specific, in which case a particular trial will be assessed.

4.3 Triggered (for cause) Inspection: Ad hoc inspections that are triggered as a result of information received by the MHRA about suspected violations of legislation relating to the conduct of clinical trials. In rare circumstances, the organisation may receive little or no notification of these inspections in advance.

4.4 Requested Inspection: Marketing authorisation application related inspections that may be performed at the request of the MHRA licensing division and conducted via national inspection procedures. Alternatively, they may be requested by the Committee for Medicinal Products for Human Use (CHMP) for applications via centralised procedures or by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).

4.5 Pre-inspection dossier: Pre-inspection documentation requested by the MHRA within 30 days of their inspection notification. This includes a list of clinical trials; organisation charts; SOP lists; contact details; overview of facilities; service providers and clinical trial activities. The GCP inspection dossier template can be accessed via https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

5. Roles & Responsibilities

5.1 The Regulatory Compliance Team (RCT) situated within the NJRO are responsible for leading on the organisation and coordination of all GCP inspections that take place within the Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH). This includes both sponsored and hosted inspections.

5.2 The RCT must inform the relevant research teams/investigators of impending inspections, and should support teams in the preparation and participation of inspections where appropriate.

5.3 If a CI, PI or study/delivery team receives notification that an external audit or inspection is to take place for a NuTH hosted study, they should inform the Regulatory Compliance Manager as soon as they become aware via 0191 2824461. Written notification should also be sent to nuth.genericqueries@nhs.net and tnu-tr.sponsormanagement@nhs.net. Any external audit findings and reports should also be forwarded to these inboxes to allow identification of trends, risks and local training needs.

5.4 The RCT are responsible for notifying the Head of the NJRO, Clinical Director of R&D and Assistant Medical Director of any forthcoming inspections. They should also notify all departments who are (likely to be) involved in the inspection (e.g. Clinical Trials Units, Pharmacy, Labs etc.) and any participating sites that have been selected as part of the inspection.

5.5 The sponsor, trial management team and study/delivery team (including CI/PI) are responsible for ensuring documentation is accurate, up to date and 'inspection ready' at all times. They should also be ready to provide necessary documentation to the sponsor for preparation of an inspection dossier or to the MHRA inspectors upon request.

5.6 The sponsor, trial management team and delivery team (including CI/PI) should also make themselves available during the inspection should they be required to provide inspectors with additional information.

6. Procedures

6.1 Planning of the Inspection (including Pre-inspection Documentation)

6.1.1 For routine national inspections, a preliminary notification is usually sent out to the organisations identified for statutory inspection 2-3 months in advance.

6.1.2 Each organisation is requested to provide a GCP 'Pre-inspection Dossier' (including a clinical trials spreadsheet) within 30 calendar days of notification. An example of a dossier checklist is provided in Appendix 1.

6.1.3 The dossier incorporates information such as:

- A record/list of clinical trials
- Organisation charts/details
- Index of Standard Operating Procedures (SOP) & processes
- Key contact details
- Overview of facilities
- Key service providers
- Clinical trial activities

6.1.4 The GCP inspection dossier assists the inspectorate in understanding how the organisation coordinates, controls and manages the conduct of its clinical trials; who within the organisation performs clinical research; and where this research is performed.

6.1.5 For GCP inspections of NuTH as a research sponsor, the dossier will include information on both NuTH sponsored and NuTH hosted (non-commercial) clinical trials of IMP.

6.1.6 The MHRA recommends using their 'GCP inspection dossier template'; 'GCP inspection dossier clinical trial spreadsheet' and 'GCP inspection dossier checklist' to ensure all the appropriate information is included. These can be accessed at: https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

6.1.7 The lead inspector will then usually review the dossier and agree an inspection date and the agenda with the organisation.

6.1.8 The inspectorate may request updated additional details nearer the date of inspection; these usually relate to data points which regularly change over time e.g. recruitment and adverse event rates.

6.1.9 A confirmation letter (or email) will be issued once the inspection dates have been agreed and will detail the logistics of the inspection, members of the inspection team and any applicable fees. The RCT should share any relevant details with all personnel and support departments involved.

6.1.10 A number of clinical trials will be selected for inspection though this can change during the inspection visit.

6.1.11 A draft inspection outline/plan will usually be provided to the organisation for review and confirmation of the personnel involved in the interview sessions.

6.1.12 It is important to ensure that interviewees are available at their allocated time. If someone is unavailable, alternative times/locations can be requested.

6.1.13 It is also important that the sponsor, CI/PI and study team ensure that all documentation requested by the MHRA is available (some of which may need to be retrieved from archive) and that they make themselves available during the inspection should they be required to provide inspectors with additional information.

6.1.14 Planning for triggered and requested inspections differ from routine inspections in that the objectives of the inspection are to answer specific questions raised (triggered inspections) or to satisfy the MHRA that a specific trial has been conducted in accordance with the legislation.

6.1.15 Triggered inspections can also be unannounced, and as such a detailed inspection plan may not be shared with the organisation.

6.1.16 For both routine and triggered inspections, GCP inspectors will often require access to various IT systems in order to access study records. These systems may include the Local Portfolio Management System (LPMS i.e. ReDA), Q-Pulse and e-Records. The RCT within the NJRO will arrange access to the e-Record system via the completion of a 'non-trust IT monitor account request' form. These can be accessed via: https://newcastlejro.com/research/resources/documents/. The RCT will also arrange access to LPMS and Q-Pulse by contacting the NJRO Informatics team.

6.2 Conduct of the Inspection

6.2.1 An opening meeting is usually held on the first day of the inspection whereby the scope, purpose and conduct of the inspection will be described. The inspection will generally be conducted in accordance with a predetermined plan, though this may be revised based upon inspection outcomes.

6.2.2 The MHRA may be interested in various processes, some of which may relate to regulatory submissions; laboratories; IMP management; contract management; project management; documentation (including Trial Master Files/Investigator Site Files); quality assurance; training; computer systems; monitoring & oversight; pharmacovigilance; medical advisors; data management; statistical analysis; report writing; archiving; and investigational sites.

6.2.3 The inspection would usually consist of a site visit to the organisation (i.e. sponsor and CTU where applicable, including relevant support departments where requested – e.g. pharmacy, laboratories, archives etc.) and, if appropriate, visits to one or two investigator sites involved in the organisation's current trials.

6.2.4 Interviews with relevant personnel are usually conducted, as set out in the inspection plan. Interviewees shall answer MHRA inspector's questions honestly and succinctly to the best of their knowledge. All interviews shall be attended by a scribe to record the discussions.

6.2.5 Interviewees are able to update or clarify information given during an interview at any time throughout the inspection. However this should be done via the team coordinating the inspection (i.e. the RCT).

6.2.6 The inspectorate would also usually review documentation such as the Trial Master File (TMF) for the selected clinical trials or any other documents that have been requested during the inspection.

6.2.7 Inspectors may also request to see certain documentation using document request forms. The RCT would coordinate the retrieval of these documents and confirm with the inspector once the documents have been provided. A record shall be kept of any documentation provided. Failure to provide the requested documentation will likely result in a report finding.

6.2.8 The inspector may also visit facilities involved in clinical trials (e.g. archiving facility, pharmacy, labs etc.) and these visits may be pre-arranged as per the inspection plan or decided upon during the inspection. MHRA inspectors shall be accompanied at all times during visits to relevant departments and inspectors shall adhere to any health and safety guidelines regarding entry in to restricted or high risk areas (e.g. consider hand washing; personal protective equipment etc.).

6.2.9 During the inspection, the inspection plan may be deviated from if the results of the inspection or unforeseen circumstances warrant this.

6.3 Close out and Reporting of an Inspection

6.3.1 A close out meeting will usually be held on the last day of the inspection at each site, where the inspectors will provide verbal feedback on any deficiencies identified and if necessary, information on any further sites to be inspected.

6.3.2 The inspection report will specify the criteria used to categorise findings. However deficiencies identified during MHRA inspections are usually classified as 'critical', 'major' or 'other':

Grading of Inspecting Findings	
Critical	Where evidence demonstrates the occurrence of significant and unjustified departure(s) from applicable legislative requirements with evidence that: • The safety or wellbeing of trial subjects has been or has significant potential to be jeopardised; and/or • The clinical trial data are unreliable; and/or • There are numerous major non-compliances across areas of responsibility, indicating a systematic quality assurance failure; and/or Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported major non-compliances.
Major	A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed in to a critical issue, but may have the potential to do so unless addressed, and/or 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.
Other	Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or GCP has occurred, but it is neither critical nor major.

6.3.3 The lead inspector will prepare an inspection report after the last site visit or on receipt of the last document requested, whichever is latest. This report is then reviewed internally within the MHRA to ensure consistency of deficiency classifications; therefore the grading of a deficiency may change from what was initially communicated at the closing meeting.

6.3.4 Alongside those deficiencies classified as critical or major, relevant references to the regulations will be provided.

6.3.5 The inspection report will be sent to the inspected organisation (i.e. the sponsor and CTU where appropriate) usually via email. The report will not be sent to NHS trusts associated with the selected investigator sites, unless there are specific data or subject safety issues identified.

6.3.6 Usually, critical findings require an agreed remediation plan to be put in place and re-inspection can occur if necessary. Major findings must be addressed but the

organisation suggests to the MHRA how this is achieved. Other findings do require remedy where this is possible, and preventative actions should always be considered.

6.3.7 If there are critical findings identified the MHRA GCP inspectors will refer these to the GCP Inspection Action Group (IAG) which oversees all critical findings and decides on the actions to be taken in addition to the review of CAPA for the critical finding. Post inspection actions that the IAG may consider include quarterly reporting, early re-inspection, referral to relevant stakeholders (e.g. other regulators/agencies; Health Research Authority; General Medical Council; Care Quality Commission), suspension of Clinical Trial Authorisations and in serious circumstances, an infringement notice or prosecution.

6.4 Responding to Inspection Findings

6.4.1 Following receipt of the inspection report, the organisation is requested to respond to any deficiencies identified and provide the MHRA with an appropriate 'Corrective and Preventative Action' (CAPA) Plan. The lead inspector will set the response deadline; this is usually 30 calendar days.

6.4.2 If the inspector identifies a deficiency that requires urgent action (e.g. to protect trial subjects), the inspected party may be requested to take immediate corrective actions.

6.4.3 A dialogue may be held with the MHRA to clarify findings and proposed CAPAs. The final written response to the MHRA shall document CAPAs and associated timelines.

6.5 Close out of the Inspection

6.5.1 After reviewing the organisations responses to the findings identified, once the MHRA are satisfied with the response they will formally accept the CAPA plan and issue a GCP inspection statement and a letter/email to formally close the inspection.

6.5.2 This will include any comments the inspector wishes to make (e.g. such as the requirement for the organisation to provide quarterly reports on their CAPA progress in order to demonstrate that appropriate action is being taken).

6.6 Post Inspection Follow Up

6.6.1 An overview of the inspection (along with any relevant updates) shall be disseminated to all relevant teams/study personnel (including but not limited to the Clinical Director of R&D, Assistant Medical Director, Head of the NJRO, Quality Assurance Team and all relevant study teams/support departments). Updates may be provided by the RCT via email or via discussion at the applicable senior management meeting.

6.6.2 Any CAPAs in relation to inspected projects shall also be discussed with the CI, trial management team and study team where appropriate.

6.6.3 Any CAPAs in relation to sponsor oversight systems/procedures at NuTH shall be addressed by the RCT, liaising with Sponsor Pharmacy, the wider NJRO and any other relevant support departments where appropriate.

6.6.4 The appropriate close out of all CAPAs shall be overseen by the RCT for all NuTH sponsored studies. For hosted studies, CAPAs will be overseen by both the RCT and Governance team.

7. References

Medicines and Healthcare Products Regulatory Agency (MHRA, 2012) Good Clinical Practice Guide. Pg. 465-480.

Research and Development Forum (2011) 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. Accessed via: http://www.rdforum.nhs.uk/content/wp-content/uploads/2014/07/RDFguidance.pdf

A summary of the MHRA GCP Inspection Process can be found at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/420781/GCP-flowchart.pdf

https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

8. Appendices

Appendix 1: Example of Dossier Checklist

Appendix 1: Dossier Checklist (Example)

Medicines & Healthcare products Regulatory Agency

MHRA

GCP Inspection Dossier checklist

Please use this checklist to ensure you have included all the relevant documentation in your GCP Inspection Dossier before submitting it to the MHRA.

Organisation Name:	

GCP Inspection Dossier Requirements	✓	**Comment *(If required)***
1 x electronic format (as bookmarked PDF plus excel spreadsheet for section 3 and 5 and section 2 item 3)		
Section 1		
Item 1 – Organisation Charts (Staff names present)		
Item 2 – List of clinical trial processes (i.e. a list of all your Policies/SOPs/Work Instructions)		
Item 3 – List of all computer systems & validation status (as excel spreadsheet)		
Item 4 – For non-commercial organisations only		
Item 5 – List of clinical trials (as excel spreadsheet)		
Item 6 – Significant changes since the last inspection		
Section 2		
Item 1 – Organisation details in UK		
Item 1 – Primary contact details: name, job title, telephone number and e-mail address		
Item 1 – Activities at the site identified		
Item 2 – Organisation outside UK		
Item 2 – Activities and location at the site(s) identified		
Item 3 – Delegated Tasks to Third Party Service Providers (as excel spreadsheet)		
Item 4 – Contract and Agreement Preparation		
Item 4 – Regulatory Affairs		
Item 4 – Quality System		
Item 4 – Quality Assurance		
Item 4 – Project Management		
Item 4 – Clinical Trial Monitoring		
Item 4 – Pharmacovigilance (including medical expertise, if applicable)		
Item 4 – Investigational Medicinal Products		
Item 4 – Data Management		
Item 4 – Statistics		
Item 4 – Clinical Trial Reporting		
Item 4 – Computer Systems		
Item 4 – Trial Master File		
Item 4 – Archiving		
Item 4 – Clinical Facilities		
Item 4 – Laboratories		
Item 4 – Equipment maintenance		

GCP Inspection Dossier Checklist (Version 4, Jul 2016)