Good Clinical Practice (GCP) Inspection Preparation and Conduct;
Guidance for Clinical Trials Units

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Disclaimer

This document is for guidance only. It is not intended to replace information or advice from the MHRA.

It is recommended that CTUs check advice and guidance issued by the MHRA via their website, blogs, and other supporting channels regularly, and register for MHRA updates, to be aware of current guidance.

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Section 1 Introduction

This guidance document was written in response to a request by the UKCRC Clinical Trials Units Network Executive Committee to provide support in the preparation of Clinical Trials Unit (CTU) staff for Medicines and Healthcare Products Regulatory Agency (MHRA) GCP Inspections and to share best practice in this area. It has been written to provide practical advice to academic CTUs involved in the design and conduct of single-site and multi-site clinical trials of investigational medicinal products (CTIMPs) and may be useful for other organisations performing a similar role. It is specifically aimed at the individual(s) working within a CTU who are/will be responsible for leading the preparations for MHRA inspections of CTUs. The guidance was updated in 2021 to include reference to the conduct of 'remote' inspections and following the UK's exit from the EEA, the revision history can be found in Annex 1.

ICH GCP describes inspection as "*the act by regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (ies)*

The concept of and techniques applied through Good Clinical Practice (GCP) inspection are not unique to clinical trials. The purpose of any inspection is, in an organised way, to evidence and evaluate the quality and compliance of an activity. Ultimately, therefore, the purpose of statutory GCP inspection is to demonstrate regulatory compliance with current regulatory requirements for clinical trials; inspection is not about fault finding or blame. It is important to note, however, that the MHRA Inspectorate recognise that the drivers for conducting non-commercial trials and therefore the risks associated with regulatory compliance can be quite different to those associated with commercial trials, for this reason statutory GCP inspections of non-commercial trials are performed by inspectors with specialised training and experience in this area.

An inspection is an opportunity for critically appraising and showcasing the capabilities and experience of the CTU and for gaining further regulatory insight; it can also be helpful in raising the profile of and maintaining a high profile of clinical trials research within the host institution. Inspections and resultant findings can provide an opportunity to raise quality standards within a CTU.

Section 2 MHRA Inspection

2.1 The Legal Basis for MHRA Inspection

The Medicines and Healthcare Regulatory Agency (MHRA) is the competent authority that regulates CTIMPs in the UK. The Medicines for Human Use (Clinical Trials) Regulations 2004[1] (Statutory Instrument 2004 No. 1031) grants statutory powers to the MHRA to undertake routine and triggered Good Clinical Practice (GCP) inspections of Sponsors and other organisations conducting clinical trials of investigational medicinal products (CTIMPs). The Medicines for Human Use (Clinical Trials) Regulations are commonly referred to as 'the Regulations'.

Notably the MHRA have the power to inspect clinical trials which do not hold a Clinical Trial Authorisation as a CTIMP but are suspected to fall under the Medicines for Human Use (Clinical Trials) Regulations[1]. This enables the MHRA to inspect trials where an error has been made regarding whether a clinical trial authorisation is required under the Regulations[1].

The MHRA powers of inspection for clinical trials extend to manufacture, pharmacovigilance, and distribution against Good Manufacturing Practice (GMP), Good Pharmacovigilance Practice (GPvP) and Good Distribution Practice (GDP). The MHRA also includes the Good Laboratory Practice (GLP) Monitoring Authority which inspects studies conducted in support of health and environmental safety associated with chemicals, pesticides, pharmaceuticals, food, and feed additives. Occasionally inspectors from other GXPs and other MHRA staff may attend an inspection to provide technical support to the inspection team or for internal development purposes.

2.2 Types of MHRA Inspection

MHRA GCP inspections can be conducted on-site (e.g., at the Sponsor, CTU offices or at trial sites) entirely remotely or as a hybrid model combining the two.

Remote inspections typically involve document requests made prior to the inspection alongside access to electronic trial master files where these are used so that the documentation is available and ready for review on day one of the inspection. Additional documentation would be requested as the inspection progresses.

Office based inspection evaluation and risk assessment activities may also request documentation be provided but as part of an inspection they may be used to review information held within the MHRA, follow up on information within the inspection dossier, review of trial protocols and reports, and undertake any necessary training etc. Office based inspection evaluation and risk assessment activities

do not replace inspection days as they are primarily used in addition to inspection activities and can also be used outside of an inspection to follow up on issues. The use of Office based inspection evaluation and risk assessment activities will be discussed by the lead inspector if these are required to support the conduct of the inspection.

The three main types of GCP inspection in relation to the Regulation are:

Statutory GCP Inspection

The UK statutory GCP inspection schedule is developed using a risk-based approach. It uses a combination of information from various sources, both within the MHRA and from outside the MHRA.

Statutory GCP inspections can be systems based, trial specific or a combination of both. A CTU inspection will usually be focussed on the CTU processes such as project management, data management, statistics, reporting, computer system validation and trial monitoring. Any clinical trial conducted since the implementation of the Regulations in 2004 has the potential to be selected for inspection, although it is usual that trials conducted since the organisation's previous inspection will be chosen.

On occasion a CTU Statutory GCP inspection may lead to a follow-on inspection at an investigator site, central laboratory, or contracting partner however usually this will be conducted separately to the CTU inspection but will be included in the inspection report. The inspectorate generally allows a minimum of six-weeks between the point of notification and an investigator site inspection taking place. This is to allow for appropriate changes to clinical commitments to be made to facilitate the attendance of the Principal Investigator. Investigator site inspections usually take 1.5 – 2 days to conduct.

Triggered Inspection

Triggered inspections are instigated when concerns relating to the conduct of a clinical trial have been received by the MHRA which suggest that expedited on-site follow-up is required. Depending upon the nature of the information received (which may come from e.g., serious breach notifications, whistle-blowers, other MHRA departments or other organisations such as the HRA) the MHRA may give short notice or no notice that a triggered inspection is to take place. Where notification is

provided to the organisation this will be via email from the lead inspector and usually followed up by a phone call to discuss the inspection scope and required information. If no notice is given of an inspection, then the lead inspector will present the organisation with a written notice of inspection on arrival.

Requested Inspection

Whilst these are not common in the non-commercial environment, the inspectorate may conduct inspections on behalf of MHRA assessors or colleagues from other competent authorities. These usually take the form of a trial specific inspection and do not focus on the systems in place at the organisation. Notification of requested inspections is usually via the lead inspector and requests for information prior to the inspection are likely to focus on the conduct of the concerned trial e.g., copy of the clinical study report rather than requesting an inspection dossier.

2.3 Scheduling of Statutory GCP Inspections

Each organisation is allocated a risk score (high, medium, or low) which is used to prioritise the allocation of inspections, with the schedule being adapted as necessary as new referrals and intelligence are considered. Such information includes previous inspection history, number, and nature of CTIMPs conducted by an organisation, follow-up inspection requirements associated with MHRA Inspection Action Group referrals, serious breach referrals, whistle-blowers, and other forms of intelligence.

Organisations to be inspected are selected on a quarterly basis with the organisations with the highest score at that time being more likely to be selected for inspection. This does not mean an organisation with a low score will not be selected; organisations running lower risk trials or where CTIMP activity has ceased but was ongoing since the last inspection are still eligible for inspection.

The MHRA identifies and notifies more organisations than it intends to inspect per quarter to ensure that a sufficient pool of organisations to be inspected exists and have been given appropriate notice. It should also be noted that the schedule is regularly reviewed by the inspectorate, and this may lead to reprioritisation of inspections or reallocation of inspector resource based on urgent inspection requests. This does mean that not all organisations are inspected within the next 3 months, but those organisations previously notified are prioritised for the following quarter.

2.4 Notification of Statutory GCP Inspections

Statutory GCP Inspections will typically be notified to the MHRA contact for the organisation by email, titled 'Advance Notice of MHRA Statutory GCP Inspection'. Usually at least 3 months' notice will be given in advance of the planned inspection date. The inspection notification will describe the required timelines for communication with the inspectorate and include a request for further information to be sent to the MHRA within 30 days. The information will be in the form of an *Inspection Dossier* and *Clinical Trials Spreadsheet* (Section 4.3); for which templates are available on the MHRA website (these are periodically updated so the organisation should check they are using the current version). It is recommended that the CTU familiarises itself with these documents ahead of notification.

Following provision of the completed dossier to the MHRA it is common that additional information is requested from the CTU during the set-up of the inspection, which is to be provided prior to or at the start of the inspection. At the point of receiving the inspection notification the inspector will not have finalised the scope of the inspection; they will use the information provided to them in the dossier, and from other information held by the MHRA, to determine the scope of the inspection.

The actual date of the inspection will be negotiated and agreed with the Lead Inspector following review of the inspection dossier. It is strongly recommended that any challenges the CTU faces with proposed dates and the inspection plan are discussed as early as possible with the Lead Inspector. The MHRA are amenable to making reasonable adjustments to facilitate the involvement of key individuals in the inspection such as using electronic conferencing software, moving the timing of sessions or, if necessary, moving the dates of the inspection (where possible).

Where an organisation has not been notified of a date for inspection within 6 months of submission of a dossier, it can be assumed the organisation has been re-prioritised for the following inspection period. The lead inspector could be contacted to discuss anticipated timelines.

2.5 Paying for an Inspection

Details of inspection costs and payment instructions are included on the MHRA website. The inspection fee is based on a daily rate per inspector., with different daily rates for inspections (on-site and remote inspections are charged at the same rate) and office-based evaluation and risk assessments. Additional sites requiring inspection will attract an additional fee (for each site visited) and where inspection is required in another country, the organisation will be required to meet subsistence and travel costs.

It is advisable to agree up front with the host organisation and sponsors which organisation will be liable to pay for the MHRA's fees for inspection.

Section 3 CTU Culture and Practice

> **Being inspection ready means adopting simple good practice into the day-to-day processes and culture of the CTU which not only helps with the smooth running of each trial but can also minimise the preparatory work following notification of an inspection.**

There can be several years between inspections, but it is critically important to ensure staff remain aware of basic standards of good practice along with changes to legislation and applicable guidance to ensure ongoing regulatory compliance which can be demonstrated at inspection. Being prepared up front will also reduce the amount of time required to prepare the dossier and can free up valuable time for other inspection preparation activities; it also minimises the risk of inaccurate information being presented to the MHRA. The dossier assists in the development of the plan for an inspection, so errors and inaccuracies have the ability to lead to extension of an inspection if the information is found to be wrong and has impacted on the areas selected for review.

Trial Master File (TMF), electronic Trial Master File (eTMF) & Essential Documents

Trial Master Files may be entirely on paper, entirely electronic or a hybrid of both. Other systems including central systems may exist that hold essential documents (e.g., central email repository, SOP management system, central training records) relevant to the trial and should therefore be considered as part of the TMF[2].

eTMFs are validated document management systems with the following controls and security features:

- User accounts created and deleted with a formal user approval and training process.
- Secure passwords for users
- A system for locking/protecting individual documents or the entire eTMF to prevent changes to documents
- Regular back-up

- Use of digital signatures
- Role based permissions
- Audit trails.

Where documents are stored electronically on CTU servers (i.e., server is used as a document repository rather than a validated document management system), processes should be in place to ensure clear structuring and indexing of the essential documentation on the servers and reference to the location of the documentation should be included in the paper TMF.

Whether the TMF is paper or electronic, an evidence trail (also referred to as the audit trail or document trail) must be maintained in a format which is accessible. A good evidence trail will include documentation which helps 'tell the story' of the trial e.g., documents which describe the handling and decision making associated with notable issues, disagreements etc. These documents are often very helpful for day-to-day management of the trial and handover as well as demonstrating that the organisation was acting appropriately at the time; a convincing evidence trail of regulatory compliance will not be able to be 'pulled together' once an inspection notice has been received. Activities which support 'being inspection ready' in this context include:

- ✓ Timely filing of documents in the paper and/or electronic TMF ideally contemporaneously with the events being evidenced.
- ✓ Where using electronic source documents as part of the TMF; ensuring there is a clearly documented definition of which documents are considered to be 'source' and where these documents are held.
- ✓ Where different parts of the TMF are held by different parts of the CTU or by a different organisation; ensuring there is a clearly documented process to describe how each section of the paper and/or electronic TMF is updated, by whom and when. Names and addresses of each organisation involved must be kept up to date to allow the TMF sections to be pulled together in one place, where this is necessary for the inspection, even where they are located overseas. Usual practice by the MHRA Inspectorate is to review the conduct of the trial at the organisation undertaking the work therefore essential documents will usually be reviewed in-situ.
- ✓ One of the risk points in any clinical trial is handover; trials can run over several years and there are therefore likely to be staff changes during the lifetime of a trial. Considering how handover of responsibilities will be managed and documenting handover notes within the TMF can evidence how well handover risks were managed.

✓ Ensuring the paper and/or electronic archiving processes consider timely access for inspection purposes. This is particularly important when using 3rd party archive providers to ensure any contracts permit timely retrieval of documents and electronic data and are permissive of MHRA direct access to premises for inspection purposes.

Staff Training

Personal development opportunities including training are a key feature of any quality-controlled environment, enabling staff working on clinical trials to improve their skills, knowledge, and experience. Any person involved in the conduct of clinical trials must be qualified and able to demonstrate competence to perform their tasks as evidenced through qualifications and/or training. In this context being inspection ready can include:

✓ Ensuring mandatory, routine staff training is provided according to the CTU policy/SOP and evidenced in the individual staff members' training record.

✓ Adopting systems for central monitoring (and remote monitoring where needed), escalation, and intervention where individual staff training is not up to date.

✓ Ensuring staff keep their individual training files up to date according to the CTU policy/SOP e.g., through review by the line manager and/or internal audit/QC checks.

✓ Ensuring the training record policy/SOP includes the requirement for retention of a training records when a member of staff leaves the CTU.

✓ Provision of training for new and current staff to maintain awareness of the Clinical Trial Regulations and GCP relevant to the individuals' role.

Quality Management System

A formalised system for documenting policies, processes, and responsibilities for ensuring quality and compliance with the Clinical Trials Regulations is a basic requirement of registration for any UKCRC Registered CTU. Different quality assurance processes for monitoring compliance with regulatory requirements and SOPs exist across CTUs and various examples of these processes are available on the UKCRC CTU Network website. The following activities may be deemed appropriate depending upon the size and risk of the CTU's portfolio and features of the QC/QA function:

✓ Where audit and monitoring feature; ensuring all quality check, audit and monitoring actions are dealt with in a timely manner.

- ✓ Ensuring any previous inspection findings and corrective and preventative actions are actioned in a timely manner in accordance with the timelines agreed with the MHRA.
- ✓ Including systems audits to identify any issues with completion of staff training records.
- ✓ Applying risk adaptation to any internal audit programme. Some factors may increase the scrutiny on the trial such as poorly handled serious breaches, use of the trial in a regulatory submission or high impact and publicity of the trial following publication. Whilst other factors may decrease scrutiny such as good evidence of compliance on another trial led by the same team, where the same team of staff are working on multiple trials, type A (low intervention) trials.
- ✓ Conducting and documenting gap analyses to identify where potential issues may lie. This demonstrates intended changes, even if not yet implemented fully.

Ideally well-defined systems and processes and clear lines of reporting should be balanced with a supportive ('non-blame') culture when errors are identified.

CTU Operations and Activity

As CTUs grow and develop over time, operational structures including lines of communication, reporting and accountability will need to be reviewed to ensure these remain effective. Information regarding the operational structures and activities of the CTU will form part of any inspection dossier, it is therefore pertinent to consider how documentation and logs for day-to-day operational activities can be used in any required inspection preparation. Some CTUs choose to prepare information for the inspection dossier up front and update it on a set schedule or as new information is available or embed data collection into QC processes. Whether this is the case or not, the CTU's inspection preparation system must facilitate the accurate collation of information within an acceptable period of time to meet the MHRA's timelines. Where there is a risk key data items may not be available within the timeframe for completing the dossier, mitigation plans should be initiated, such as frequent maintenance of operational data on a centrally held log/database e.g., within QA. Maintenance of the following information regarding CTU activity can be helpful and make inspection preparations easier:

- ✓ List of all CTIMPs.
- ✓ Details of information systems and services. Direct access to systems that make up the TMF and clinical trial support systems (e.g., QMS eSystem) will be required, therefore, consider how inspectors can access information systems, particularly during a remote inspection.
- ✓ Contact details for key organisations and individuals outside the CTU/host institution who need to be notified that an inspection is scheduled to take place (this information may be

particularly helpful in the case of a triggered inspection where the timelines between notification and the inspection taking place may be quite short).

✓ Contact details for key individuals within the CTU and host institution where they would be required to provide information for the inspection dossier. It is helpful to build relationships and raise the profile of inspection within the host organisation to ensure information and appropriate support is available promptly following an inspection request.

✓ Operational information such as organograms and organisation structures which will be required to be provided as part of the inspection dossier.

Information from External Sources

It is advisable to maintain an up to date understanding of regulatory expectations. Sources of information include but are not limited to those documents listed under Additional Reading.

Where the host institution is responsible for providing infrastructure used by the CTU in the conduct of CTIMPs (a common example being in the provision of IT and telecom systems), it is essential that systems are in place to ensure that the host institution inform the CTU, with sufficient advance warning, of proposed changes to the services provided to enable any risks to be assessed and change management to be managed, as appropriate.

Participant Information Sheet/Informed Consent Document

Remember to ensure that the Patient Information Sheet/Informed Consent Document template includes a statement whereby participants are notified that relevant sections of their medical records, and data collected during the study may be accessed by the Inspectorate for the purpose of monitoring the safety and regulatory compliance of the trial. Failure to include this statement does not prevent the inspectors from reviewing the TMF but will result in an inspection finding if participant consent is deemed inadequate.

Section 4 Actions Following Notification of an Inspection

*The following section focusses on preparing **for a Statutory GCP Inspection of a Clinical Trials Unit**. The same preparatory actions may be applicable for a Triggered Inspection, where sufficient notice has been given, however the focus of these by their nature are usually narrower and therefore some of the steps may not be applicable.*

For CTUs undergoing their first inspection some have found the following to be helpful in preparing for the inspection, although if applying principles and practice in order to 'be inspection ready' these additional preparations may not be necessary:

- Speaking to other CTUs about their inspection experience.
- Meeting with key staff to highlight/escalate any issues which are causing them concern.
- Paying for an external auditor, mentor, or trainer (specific knowledge in remote inspections may be desirable).
- Including trials selected for inspection in the internal audit programme, where sufficient time and resource allows.

4.1 Agree an Inspection Lead and Project Team

A named individual, ideally independent of the trial team and with dedicated time and adequate support (both from a workload and personal perspective) to plan and manage the inspection should be identified immediately. In most cases this would be the individual with senior responsibility for Quality Assurance within the CTU.

Typically, the Inspection Lead for the CTU will take responsibility for the following:

- Point of contact with the Lead Inspector regarding the dossier and inspection preparations (on-site or remote inspection).
- Verifying the type and scope of the inspection (i.e., routine or triggered and adjusting the inspection preparation plan and communication plan accordingly.
- Working with the Inspection Project Team (or similar) to develop an inspection preparation plan (covering sections below), regularly reviewing the plan including oversight of any delegated actions and providing regular reports to the CTU's senior management team.

An Inspection Project Team should be established with a senior representative from each relevant department or team within the CTU. Each member of staff must be in a position to make decisions regarding prioritisation of work within their department or team in preparation for the inspection and will act as a key line of communication between the Inspection Project Team and individual staff within the CTU. Where there are staff available with previous experience of inspection consider including them in the Inspection Project Team.

The CTU inspection should stand-alone and should not include responsibilities of the host institution unless specifically agreed with the Lead Inspector. Where shared functions exist between the host institution and CTU, for example use of a shared quality management system or contracting arrangements these should be highlighted to the Lead Inspector. In such cases it may be appropriate for relevant members of the host institution to be part of the Inspection Project Team.

4.2 Develop a Communication Plan

Communicating with the MHRA Lead Inspector

Agree one person who will be the point of communication with the MHRA; typically, this would be the Inspection Lead but may be another senior member of staff such as the Director. A back-up should also be identified in case of staff illness or absence to provide continuity.

Communicating Inspection Preparation Progress to CTU Senior Management

The Inspection Lead should report progress on the inspection preparations to relevant CTU senior managers regularly e.g., on a weekly basis to facilitate a co-ordinated approach to planning activities and allow early escalation of issues.

Communicating to CTU Staff

Although expected to be 'part of the job', staff react differently to the prospect of inspection, whether or not they are directly involved. A good communication strategy, informing groups of staff as well as individuals about the likelihood of involvement in the inspection or preparation for the inspection can be helpful in managing expectations and workload priorities. Ultimately it is important to ensure the day-to-day business of the CTU can continue and remains largely unaffected by the inspection and related preparation.

Notifying the Host Institution, External Organisations, and Individuals about the Inspection

The Inspection Lead (or delegate) should notify relevant individuals/organisations that an inspection is scheduled to take place and an approximate timeframe for the inspection. The following list is not exhaustive, and each inspection is different therefore as a basic principle in developing a communication plan the Inspection Lead should consider who should be notified of what, at what time point and which method of communication will be best.

Host Institution: There may be specific routes of escalation/notification within the host institution to consider such as the research office, hosted IT services or laboratories.

Chief Investigators, Sponsor(s), Funders, and other contracting partners: In many cases the CTU's host institution will also be sponsoring the research however this is not always the case. In some cases, contracts between the CTU and contracting partner may include specific clauses that specify timelines for the CTU to notify the contracting partner about the inspection or require a representative to be present at the inspection; the Inspection Lead should check to ensure all contracts are being complied with.

Investigator sites: Investigator sites will not necessarily be included as part of a CTU inspection; however, one may be scheduled to assess how the monitoring, oversight, and communication activities of the CTU can be demonstrated in the 'real world'. This would be conducted as a separate inspection usually about 6-8 weeks after the CTU inspection. Therefore, it is not necessary to prospectively notify each trial site of the CTU inspection.

Where many notifications need to be made or information collated from 3rd parties, it can be more efficient to prepare template correspondence/data collection sheets. It is helpful to remind those completing requests to keep information factual.

Communication during the inspection

Consider how best to keep CTU staff engaged and informed throughout the inspection, such as providing updates as to how the inspection is proceeding and organising a formal debriefing to staff at the end of the inspection. For remote inspections consider plans for communications back-up (e.g., technical or Wi-Fi issues) and clear lines of communications for those directly and indirectly involved.

Communication after the inspection

The Inspection Lead should agree with the senior management team all relevant parties (individuals and organisations) to whom the Inspection Report will be provided in full and what communication will be made more widely.

4.3 Completing the Dossier and Clinical Trials Spreadsheet

As part of the inspection notification a dossier describing the structures, function, and activities of the CTU and how the CTU interacts with the host institution will be requested along with a list of all CTIMP activity in the UK since the CTU's last MHRA GCP inspection or at a minimum over the last 3 years (whichever is greater). It is important to carefully check the categories used within the clinical trials

spreadsheet to ensure individual trials are allocated and reported accurately and consistently. For example, the Clinical Trials Spreadsheet asks for trials to be categorised into:

- Planning – submitted to the MHRA but not yet open to recruitment.
- Live –open for recruitment.
- Temporary halt – to whole trial (if specific aspects of a trial are halted then a brief description should be stated in the reason for temporary halt box).
- Completed – any trial which has submitted its end of trial declaration.
- Reported –completed all regulatory reporting and now archived.
- Terminated early (with reason).
- Submitted – submitted as part of a licence application.

Suggested checklist for preparing the inspection dossier

- ✓ Produce a basic Gantt chart (project plan), or similar, for the tasks relating to completion of the dossier, working back from the final date that the submission is due – e.g., day 1 assign tasks to relevant parties, day 2 run all reports and cleanse data, day 3 send data requests to all identified investigators.
- ✓ Agree and notify the individuals/organisations that will be responsible for collecting and collating dossier data and completing each of the sections of the dossier – this is likely to include several individuals responsible for their own sections, with oversight from the Inspection Lead.
- ✓ Allow sufficient time for individuals to provide the required information and sufficient time to cleanse and review the information and final dossier prior to submission. Build in contingency time to cover unexpected delays and issues which arise.
- ✓ Take care to ensure that the details contained within the trial spreadsheet are accurate.
- ✓ Identify one individual to format the application according to the standards required by the MHRA for submission – details can be found on the MHRA website[3].
- ✓ Ensure regular updates are provide to the Inspection Project Team and senior management team and escalate any issues immediately.
- ✓ Agree a process by which the final dossier will be reviewed and who(m) within the CTU will be responsible for the final sign off and submission of the dossier; this may be the Inspection Lead and/or Director, for example.
- ✓ Check the new dossier with previous inspection dossiers submitted by the Host Institution and CTU to ensure that nothing relevant has been missed.

✓ Use the GCP inspection dossier checklist, available on the MHRA website, to ensure all the relevant documentation has been included in the inspection dossier before submitting it to the MHRA.

The dossier should demonstrate that there are clear and robust lines of reporting and escalation with well-defined roles and responsibilities within the CTU and with the host institution and other contracting partners; this can be provided in the most suitable form e.g., organograms, diagrams.

The dossier is required to be completed and returned to the Lead Inspector within 30 days of the inspection notification. Information provided in the dossier will be verified with other information held by the MHRA, document review and interviews during the inspection, it is critical that any information provided is accurate and complete. Therefore, once the dossier has been provided, if aspects of the dossier content change prior to the inspection the Lead Inspector should be notified, and updated information provided.

Remember; the inspectors may call 24-hour medical information or un-blinding lines ahead of an inspection, to test the facility.

4.4 Agreement of the Inspection Plan

On receipt of the inspection dossier, the Lead Inspector will review the dossier and ascertain whether the information supplied is sufficient to enable planning of the inspection. The Lead Inspector will determine whether an inspection is still required based on the information provided (e.g., where no CTIMPs or related regulated activities been conducted by the CTU since the last inspection, an inspection may not be required). It is therefore important to ensure that any information which may affect the decision to inspect be clearly stated in the dossier and covering letter; any errors or omissions may impact on trial selection or inspection conduct.

The Lead Inspector will formulate a draft plan for the inspection which will include:
- The number of inspection days required and the number of inspectors. The length of the inspection and number of the inspectors will depend on the reason for the inspection, the type and scope of the inspection, and the size and complexity of the CTU. CTUs should expect there to be at least two inspectors present/involved, and inspections to last on average three

to four days. Inspectors in training may occasionally accompany the team of inspectors, however the CTU would not be charged for the attendance of the additional trainee.

- A schedule for each day detailing the activities which will be included in the inspection plan. About 2-4 weeks before the inspection the details of any trials selected by the inspectors for detailed review will be provided, although it is important to note that changes can be made by the Inspectors at short notice, even during the inspection.

- Remote Inspections may stretch over a number of days (not necessarily consecutive) and will require the timing of teleconferences to be agreed and set-up. The MHRA will usually host a Microsoft Teams site where documents can be uploaded and use MS Teams for interviews, facility visits and discussions. If this is considered unsuitable then this should be discussed with the Lead Inspector. It should be noted that the MHRA hosted site is the MHRA preferred option. Details regarding the use of MS Teams will be provided during the inspection set-up phase.

There is no such thing as a standard inspection schedule, however an inspection plan will typically include:

- **Opening meeting**
- Interviews
- Document review:
    - TMF/trial documentation
    - SOPs
    - Training files
- IT system reviews
- Responses from previous inspection with inspection host
- Facilities visits (if applicable)
- **Closing meeting**

Other sessions may also be included, dependant on the activities of the CTU and scope of the inspection.

The inspection schedule will be presented to the CTU Inspection Lead as a timetable, giving the proportion of time the MHRA expect to spend on interviews, document review, systems review and facility visits. The CTU will be expected to nominate relevant individuals for interview; these staff should be involved in conducting the relevant activity identified in the inspection plan. The names and

job titles of individuals involved in interviews will be required to be provided to the Lead Inspector before the inspection plan can be finalised.

By the time of the inspection a final version of the inspection plan will have been agreed and provided to the CTU by the Lead Inspector. Inspection plans should be considered a guide to the topics and times of sessions to be covered and it is common for the plan to be amended (both in terms of time and content) as the inspection progresses.

The following hints can be helpful in agreeing the inspection date and plan with the Lead Inspector:

Scheduling

- ✓ Identify institutional timelines and availabilities of key staff to allow any discussions on dates and timing of the inspection with the relevant individuals and the Lead Inspector.
- ✓ Where timelines are very tight or conflict with previous appointments which cannot be re-scheduled (e.g. for a trial being inspected, the CI has already booked to attend an international conference to present the final results of the trial or the CI is already scheduled to run a clinic and alternative cover cannot be found) raise this with the Lead Inspector to see if there is any leeway in the timing of the inspection or option for the CI to be available by phone instead.
- ✓ Identify any key staff and whether any have left or are on sick leave/maternity leave and who will be able to answer questions in their place.
- ✓ Identify additional back-up staff in case of unplanned leave, e.g., sickness, at the time of the inspection.
- ✓ Consider whether any specific restrictions need to be placed on booking annual leave over the period of the inspection and to which groups of staff this will apply.
- ✓ Identify availability of IT support staff and any planned downtime periods for relevant IT systems.

Identify appropriate facilities

Commonly the following office space will be required during on-site Inspections for:

- *Document Review*: A large room with desks and chairs. The room will need to be able to be locked during the day to provide protection to the TMFs/inspectors documents stored there.

Consideration must be given to appropriate security arrangements for the TMF overnight and whether the TMFs will need to be moved each night to a secure location.

- *Interviews*: Depending upon the number of interviews taking place at the same time, additional rooms with a table (to allow the inspector to make notes) and enough chairs for the inspector(s), interviewees and note taker (or 'scribe').

- *Show and tell sessions*: This should be considered ahead of the inspection (considering connectivity, ability to display and software access) and any special arrangements made. For on-site inspections, the use of a computer may be required to facilitate these sessions.

- *Waiting room/area*: It is helpful and can be reassuring to those being interviewed to have a supportive environment, such as a relaxed waiting room close to the interview room where they can wait prior to their interviews. This room could also be used for inspection coordination (e.g., organising the provision of additional documents for inspectors, interview preparation/maintaining lists of questions being asked).

- *Debrief room/area:* It is important for the inspection lead/project team to track issues which may arise by debriefing at the end of each interview. This also provides helpful support and reassurance to interviewees following interview, for example in case they remember something they missed or on reflection did not make sense.

- *Control Desk:* Having a single area and person responsible for day-to-day co-ordination of inspection related activities is important. This would usually be the Inspection Lead or another senior member of staff. Typically, they would take responsibility for co-ordinating the collation of additional documents requested by the inspector, ensuring interviewees are ready for their interview sessions, providing a single point of contact for staff within the CTU as well as for the Inspectors.

- *IT Logistics:* Consider the IT systems which will be needed to support the inspection plan and whether these will be available within the rooms selected for the inspection e.g., is there Wi-Fi available to access remote systems, is there a computer available to access trial email accounts or eTMF files, would computer access be helpful for staff to demonstrate trial activities in any planned 'show and tell' sessions.

Document review and interview sessions may be conducted in parallel so that inspectors can cover different areas at the same time. This also means that two, or more rooms may need to be available at a time. Ultimately if the Inspectors do not feel the room lay-outs work for them, they will move the rooms around to suit their needs.

For a remote inspection, an appropriate means of sharing electronic documentation is required. The MHRA will usually host a Microsoft Teams site where documents can be uploaded and use MS Teams

for interviews, facility visits and discussions. If this is considered unsuitable then this should be discussed with the Lead Inspector. It should be noted that the MHRA hosted site is the MHRA preferred option. Details regarding the use of MS Teams will be provided during the inspection set-up phase. Individual direct access to other electronic systems such as eTMF, ePRO etc will be required for each member of the inspection team.

Trial Master File

- To ensure compliance with regulatory requirements for provision of documentation to support inspection TMFs for the trials identified for detailed review must be made available to the inspectors. This will be either in paper or easily accessible electronic form IN THE ROOM the inspector(s) are in or via an electronic platform for remote inspection. Where email or other electronically held documents are source material consider how this can be made available to the inspector(s) in a read only accessible format e.g., through read only access to the trial email account.

- The MHRA Inspectorate recommend that when compiling the trial documentation consideration is given to whether if the inspection room were closed and no further documentation, emails or data were permitted to be submitted would the trial documentation provided be sufficient to demonstrate how the trial has been conducted?

- Where the TMF is held across multiple locations each section must be pulled together and made available for the inspector(s) IN THE ROOM at the time of the inspection or via the sharing platform for remote inspection.

- Supporting documentation and data, for example a full set of SOPs, training records for staff being interviewed, contracts and insurance policies where these are not held in the individual trial TMF must be made available IN THE ROOM at the time of the inspection or via the sharing platform for remote inspection.

Considerations for Blinded Trials

- If the trial is ongoing or restrictions remain in place regarding the blinding of a trial selected for inspection then this should be discussed with the Lead Inspector, ideally in advance of the inspection, so that appropriate steps can be implemented both by the CTU and the inspection team so as to not inadvertently un-blind staff to the treatment allocation. Consideration should be given to the provision and storage of documents; blinding status of interviewees

and people present at the inspection and management of the inspection report and responses in the event that significant issues were identified.

<div style="background-color:#5B7FBF; color:white; font-weight:bold; padding:8px;">Administration and Housekeeping</div>

- The Inspection Lead should clarify with the Lead Inspector any additional details for the day, including maps/plans for finding the premises, parking, and inspectors' requirements in regard to meals and refreshments during the inspection.
- Ensure security arrangements are robust and are made known to the inspectors.
- Identify one or two members of staff to be on call as 'runners' to respond to requests made by the inspectors for further documents or information.
- Ensure continual access to a photocopier and printer in order to provide copies of documents to inspectors upon request.
- Note-takers, or 'scribes', are a permissible and helpful addition to the inspection interviews, allowing de-brief at the end of the day to CTU senior management as well as providing useful future training material (in the form of example inspection questions).
- For remote inspections, ensure technical assistance (local/host institution) is available for the entire Inspection period to ensure appropriate access and connectivity can be maintained.

The time from notification of inspection and the inspection start may vary, depending in part on the availability of the inspectorate. Delays and postponements from initially agreed dates may occur. If there is a significant delay, some of the planning described in the sections above may need to be repeated (e.g., booking of staff time, rooms etc.).

4.5 Preparing Staff for Interview

Once the inspection dates and plan have been agreed preparations are likely to be re-focussed on the trials and staff directly involved in the inspection plan.

Where a CTU is already providing regular training to staff in good essential document management practices and being inspection ready there should be no need to provide additional training to staff whom are not directly involved in the inspection.

Staff who are to be interviewed, in particular where they have not been involved in an inspection previously, may benefit from one to one or group sessions where the Inspection Lead or another

senior member of staff asks questions relevant to the session the individual will be involved in during the inspection.

Staff should be made aware that inspectors tend to follow processes through from beginning to end and 'deep dive' into areas of interest or where issues within the selected trials have been identified. For this reason, the interview structure and questions asked will vary between organisations, and the questioning may change during an interview. Remind staff that it is acceptable to request clarification or to discuss with other colleagues before providing an answer.

Staff involved in interviews should be given clear information regarding the timing(s) and location(s) of their interview and whether there are any specific reasons to arrive early, the topic area and other people who will be involved.

For remote inspections consider how staff who have been selected for interview can best be supported during the interview process. Ensure all interviewees and other inspection attendees have access to the agreed platform for interviews and run training events in using the platform if needed.

It is important to consider how the work of staff directly involved in the inspection will be managed whilst the inspection is ongoing and all staff should be advised against using out of office messages over several days or weeks stating the MHRA inspection as a reason for not being available, an acceptable alternative would be to reference usual office cover arrangements.

It may be necessary to reprioritise the work of a small number of staff who are not directly involved in the inspection interviews to provide cover or to assist with the inspection e.g., as a 'runner' or scribe or to help cover work of staff who are involved in the inspection directly.

4.6 Working with Contracting Partners to Prepare for Inspection

Where the inspection plan includes a request to visit other facilities used by the CTU, such as internal or external laboratories, archives, trial sites and pharmacies the nature of the inspection will focus on management and oversight by the CTU of the provider (e.g., monitoring or audit of the facility, and on the data originating from the provider (e.g., trial specific inspection of laboratory data integrity). See Section 7 for recommended activities in working with contracting partners to prepare for inspection.

Section 5 What to expect during inspection

The first inspection of an organisation typically concentrates on the 'basics' (i.e., activities core to the set up and management of a clinical trial and central to the organisation being inspected). The first inspection is also usually interview-heavy with the inspectors concentrating on the systems and processes used by the organisation and how these are illustrated in the selected trials. Subsequent inspections may be data-focussed (i.e., reconstruction of a trial in greater detail) or detail-driven (i.e., reviewing aspects of a process, often across multiple trials). Subsequent inspections will also tend to involve the selection of a greater number of trials for review and less interview sessions. Inspectors may 'follow their noses' in terms of following an identified issue and this may lead to an expansion in the scope of the inspection and/or the selection of additional trials.

For remote inspections ensure all those involved in the inspection sessions have access to and are familiar with the agreed platform for meetings and interviewees prior to the start of the inspection. The structure and sessions outlined below will be similar whether for on site or remote inspections.

5.1 The Opening Meeting

The opening session is usually led by the Lead Inspector who will speak first, and will include:

- The Statutory background to the inspection.
- Introductions to the inspection team.
- Information from the Lead Inspector regarding how they intend to conduct the inspection, which may include an overview of the inspection plan, and any specific requirements which have not already been discussed prior to the inspection.
- Inspection logistics (to discuss any required changes to the plan since it was agreed – e.g., scheduling issues, illness etc.).
- A presentation from the CTU Director (or delegate) to describe the CTU structures and functions, including any changes since the last inspection (maximum 10 minutes).
- It is best to be honest about any known issues which will be identified through the inspection up front at the opening meeting.
- Housekeeping notices (e.g., fire alarm tests, toilet, and refreshment facilities).

If an alternative room (i.e., not the inspectors' room) is to be used for the opening meeting of an on-site inspection then the inspectors will normally want to go to their allocated room first before going into the opening meeting. If the room being used for the opening meeting is any distance from the

inspector's room, then it is wise to notify the lead inspector ahead of time in case this impacts on the timings in the inspection plan.

The inspection plan will state that any members of staff are welcome to the opening meeting, however it is advisable for the Inspection Lead to plan ahead who should be present based on the size of the room to ensure key staff and representatives from the host institution or other contracting partners are prioritised to attend. The opening meeting can be a good way of including staff in the inspection but where the CTU employs a large number of staff the logistics of including all staff will not be possible, or necessarily relevant.

5.2 Interview and Document Review Sessions

Sessions may vary in format but typically include:

- Interview sessions:
    - ○ trial specific interviews, with key CTU trial staff member(s) and the CI, or
    - ○ CTU process specific interviews, for example related to monitoring, quality assurance, data management, computer systems (including CSV), IMP management, PV, filing and archiving, medical writing, publication, contracts, and insurance. The sessions may be general, or a detailed 'deep dive' into the CTU systems and processes.

- 'Show and tell' sessions: These sessions are to help the inspector visualise the process. They involve practically walking through a process, e.g., by shadowing a member of staff doing the process or talking through an activity.

- Document review sessions: – Inspectors will request that they be left alone at various points during the day – particularly when reviewing documentation. For onsite inspections this means that all staff will be requested to leave the inspection room, but this should not be taken as meaning that the inspectors do not wish to be disturbed if document requests are ready or questions arise. If this is the case, then this will be notified to the Inspection Lead. During document review sessions the inspectors are left with the requested/provided documents to conduct detailed reviews, where an eTMF is provided this should be easy to navigate and access (with read only access provided). In the TMFs in addition to regulatory compliance they will be looking for compliance with the relevant SOPs.

During the inspection the inspectors will compile a list of any additional documents they require. The document request list will be handed to an interviewee at the end of each session, and periodically during document review sessions, so that the list can be photocopied, and the original returned. The

inspectors expect that the requested documents be returned as soon as possible. If there is likely to be a delay in the provision of the documents, or trouble expected in providing the required documentation, the Inspection Lead should discuss this with the Lead Inspector and an expected timeframe proposed as soon as the difficulties are identified. This allows for the delay to be considered by the Lead Inspector and for alternative documentation to be requested if necessary. This is where the control desk and the 'runners' will be most useful.

For remote inspections, different methods will need to be employed to track and provide electronic documentation quickly. The frequency for providing electronic documentation should be agreed with Lead Inspector in advance of the inspection. Typically, the document request form will be managed within the sharing platform and will be visible to all staff who have been given access.

There are different ways in which requests for additional documents could be managed; During on-site inspections document request sheets are collated centrally and numbered (the inspectors use alphabetically labelled pages) During remote inspections a running document request sheet per inspector via the sharing platform is used. Document requests are numbered (and date/time added). For on-site inspections this list can be copied and so that more than one item can be looked for at a time by different individuals. When a document is found, a copy should be made and numbered, to correspond with the relevant list. Copies of the documents should be provided to the control desk for collation. The copies of all documents on the list, can then be provided to the inspectors periodically/when available. For remote inspections, the method for labelling the documents electronically should be discussed with the Lead Inspector.

If the request is considered to constitute a significant amount of work, then the organisation's understanding of the work should be confirmed with the requesting inspector, possibly including an example, so that the inspector can confirm the piece of work is as expected to prevent wasted effort. It is recommended that a record is kept of what documents are provided to the inspectors, and when. The inspection plan will include a document deadline for the last day and every effort should be made to provide all outstanding documents by this deadline. Provision of additional documents after this deadline should be agreed with the Lead Inspector and may be refused or documentation retained for later review.

Once documents have been provided to the inspection team, they should not be retrieved without prior agreement by the Lead Inspector. If sensitive or blinded data is supplied, then the

lead/requesting inspector should be made aware so that the review can be prioritised if possible and arrangements made for the return of this information/data e.g., confidential business information or employee records. Practical solutions such as transfer of sensitive information in a sealed envelope, with an authorised member of the team member delivering it to the Lead Inspector could be considered. For remote inspections, a separate channel on the sharing platform with restricted access may need to be set-up – this should be discussed with the Lead Inspector.

- <u>Summary meeting at the end of each day:</u> At the end of each inspection day the inspectors will provide a status update from the day and provide any information or changes to the plan for the following day. The Inspection Lead should be present, be ready to provide clarifications if needed, and provide feedback to relevant members of CTU staff. It should be noted that this is not intended to be a formal debrief, but will provide an opportunity to raise significant findings, if not already raised, and to check that everything is in place for the following day or for the opportunity to check understanding.

5.3 Closing meeting

This meeting at the end of the final inspection day is to allow the inspectors to provide a summary of preliminary findings and general inspection feedback. Any grading of findings given should be considered provisional at this stage as an internal inspectorate peer review process exists. Plans for the addition of any investigator site or supplementary site inspections (e.g., laboratories) will be announced along with a request that the organisation notify the site and provide contact details for the inspectors.

The inspection plan will state that the closing meeting is open to all persons involved in the inspection, however it is advisable for the Inspection Lead to agree with the CTU senior management team whom the closing meeting will be opened up to and notify staff as relevant. If the findings are significant (e.g., critical findings) then a pre-closing meeting between the Inspectors and senior management may be requested, where it will be made known the nature of any further action such as quarterly reporting. The inspector will provide a verbal summary of the inspection findings and allow for the opportunity to correct any misunderstandings. It is important to note that the grading of the findings provided at the closing meeting are provisional and may be changed by the inspector in the final written report.

Section 6 Inspection Report

6.1 Grading of Inspection Findings

Inspection findings are graded at 3 different levels:

Critical:

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 has been or has 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 (d) and (e))

c)   Where provision of the Trial Master File (TMF) does not comply with the Medicines for Human Use (Clinical Trials) Regulations[2], as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations.

Major:

d)   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

e)   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:

f)   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.

Critical findings are escalated to the MHRA GCP Inspection Action Group (https://www.gov.uk/government/groups/inspection-action-groups) and may result in an organisation being put on quarterly reporting, early re-inspection, referral to other stakeholders, suspension of all or individual trial CTAs, issuance of an infringement notice or prosecution.

The purpose of quarterly reports is to provide the inspectorate with an update as to the progress being made against all of the corrective and preventative actions (not just those related to the critical finding), and the first quarterly report will be due 3 months from the date of the inspection statement. The quarterly reports can take any format deemed acceptable by the CTU and Lead Inspector and are submitted by email to the Lead Inspector until the corrective and preventative actions are completed to the satisfaction of the MHRA. Usually these are in the form of an annotated inspection report responses for the first few returns.

Infringement notices are rare and are issued when instances of serious or serious and persistent non-compliance with GCP has been identified. Details of these are published on the MHRA website.

6.2 Receipt of the Inspection Report

A written inspection report will be provided to the CTU within 25 working days of the last day of the inspection; where an associated site inspection has taken place the 25 days will be counted from the last day of the associated site inspection. If additional documentation has been requested to be sent on following the inspection, then the date starts from the date of receipt of the final document. A full response to the inspection report with associated corrective and preventative action (CAPA) plan will be required to be returned to the Lead Inspector within 25 days of the inspection report issue date. An organisation can request an extension to this deadline by contacting the Lead Inspector but will be asked to explain why an extension is required and what progress has been made (particularly for significant issues) on the corrective and preventative action plan to date. Extension requests should not be left to the last minute and should be made in sufficient time for the inspector to consider the application.

If there is a critical finding(s) then the Lead Inspector may issue an inspection letter focused exclusively on the critical finding for circumstances where the full report will be delayed (e.g., while waiting for a linked site inspection to be performed).

6.3 Responding to the Inspection Report

The period of time to reflect upon the inspection report findings, understand the root cause and wider impact within the CTU and develop a CAPA plan is short, therefore the Inspection Lead should consider up front how any investigations will be undertaken, who will be involved and the process for signing off the response to the inspection report e.g., review and agreement by the senior management team and/or Director. Where a letter has been issued prior to the final report, to communicate critical findings, the letter must be responded to within the deadline stipulated by the Lead Inspector for the specific issues that contributed to the critical finding.

Given their involvement in the inspection it is likely the Inspection Lead will take responsibility for all follow up actions in compiling a response to the inspection report. The following steps should be followed:

✓ *Confirm if the finding is accepted*

It is important to assess each individual finding to ensure the full meaning is understood and that MHRA's interpretation is correct and complete. Where there is further information which would be helpful for the MHRA to consider then this should be included in the response. In rare cases, where there has been a misunderstanding or misinterpretation, the (robust) evidence and justification of why the CTU does not accept the finding should be included in the response (in such cases it is advisable to discuss the issue and concerns with the Lead Inspector prior to the response being submitted).

✓ *Assess the risk and impact*

Once the findings have been reviewed and accepted the next step is to assess the findings. Evaluate whether the findings are indicative of a systematic problem or a one off. It is also important to understand the impact of the non-compliance and the risks it poses to participant safety and/or data integrity; this will be important in informing the proportionality of the CAPA. If systematic issues are identified, then CAPA should reflect how this will be managed across all affected trials.

✓ *Undertake a root cause analysis*

Determining the root cause(s) of a finding is key to minimising the possibility of it happening again. What happened, what caused it, what can be done to prevent the issue(s) happening again. Ensure that sufficient time is given for the root cause analysis to be undertaken; for more complex issues if additional time is required then this should be discussed with the Lead Inspector as soon as possible to minimise the risk of delay to the inspection report response.

✓ *Develop and document a CAPA plan*

Once all of the previous steps are complete the corrective and preventative action plan should be compiled. For each finding both corrective and preventative actions should be included unless there is justification as to why this is not appropriate. The CAPA should be specific and precise, avoiding general statements and overambitious timelines which create unrealistic expectations.

Corrective actions should consider whether the non-compliance can be fixed or at least the impact reduced. If it cannot then an explanation should be given as to the potential impact on participant safety and/or study data. Where significant issues affecting the validity of published results are found relating to trials which have already reported it is expected that corrections/retractions to published material are made.

Preventative actions should address the findings of the root cause analyses. Consideration should also be given to root causes attributed to a failure of the quality system i.e., the fact that the finding was not previously identified.

✓ *Manage the timelines and associated actions*

Timelines for corrective and preventative actions must be included in the responses and realistic in line with the amount of work to do and the available resource to do it. Where an extended timeline is given the MHRA will expect to see interim measures put in place to address the finding. Subsequent inspections review the previous CAPAs (both the work undertaken and whether the stated timelines were met) and previously identified deficiencies which have not been addressed are likely to be escalated in terms of the grading. This may also apply to findings which reoccur as this may suggest that the CAPA undertaken was insufficient or ineffective.

Actively manage the actions and proposed changes to systems and processes. The planned changes will also have a greater chance of success if supported by senior management. Measurement of the impact of changes related to the CAPA to verify that they have resolved the issue could be undertaken through the internal audit programme.

For significant findings, particularly where insufficient or untimely corrective and preventative actions have been proposed, the management of the CTU may be requested to attend the MHRA offices to explain the issue and the actions to be taken. If this is required, then this will be communicated to the Inspection Lead by the Lead Inspector.

6.4 Clarifications

The inspectors will review the responses provided and may request additional clarifications to be provided using the inspection report to indicate any clarifications required. Responses are also made into the inspection report and sent back to the Lead Inspector via email. Usually only one round of clarifications is undertaken.

6.5 Inspection Closure

Once responses have been provided and accepted by the inspection team; an inspection statement will be issued as an attachment to an email closing the inspection. The inspection statement summarises the inspection particulars and any critical or major findings. Once received the inspection can be considered closed.

Section 7 Assisting with preparation for inspection at contracting partner organisations

7.1 Where a trial managed by the CTU is selected for inspection of the Sponsor

Inspection of a sponsor will focus on the activities of the sponsor such as oversight, laboratory activities etc. and as such it may not be necessary or appropriate for the CTU to be involved unless the CTU is managing a trial which has been selected for inspection. Where a trial being conducted by a CTU is selected for sponsor inspection, it is recommended that the CTU has significant involvement, as this can reduce the number of problems encountered during the inspection or when responding to inspection findings. The nature of the CTU's involvement should be agreed with the sponsor and can include input into the preparation of the dossier, staff preparation and training, and facilitation on the day. To ensure the whole inspection process runs as smoothly as possible it is important that sponsor and CTU engage as early as possible, and that roles and responsibilities are clearly defined, and lines of communication established and understood. As CTU staff will have a more in-depth understanding of a particular trial than sponsor office staff they should be fully engaged in all preparation activity relevant to the trial, including interview training. Preparation prevents any potential for inconsistency in responses between the CTU and sponsor about trial specific details during the inspection and helps

ensure that inspection findings concerning the trial are answered appropriately. The CTU should be present at the final close out meeting and fully engaged in responding to the inspection report in regard to trial specific findings to ensure any CAPAs are proportionate and achievable.

Top tips to ensure the inspection process runs as smoothly as possible:
- Establish roles and responsibilities of CTU and sponsor office staff and lines of communication.
- Be involved in inspection preparation activities including interview training.
- Notify the sponsor office of any issues regarding the trial so there are no surprises at inspection.
- Ensure key CTU staff are nominated for trial specific interviews with relevant sponsor office staff in attendance.
- Offer CTU staff as runners or scribes for the trial specific interviews.
- Ensure the CTU QA lead or other appropriate member of staff is invited to attend the close out meeting to note any trial specific findings.
- Be involved in the preparation of the inspection report response, to ensure any CTU-related CAPAs are proportionate and achievable.

7.2 Where a trial managed by the CTU is selected for inspection of a participating site

It may be more difficult for CTUs to have direct involvement in a site inspection of a CTU managed trial, particularly where the trial is one of a number being selected for inspection at the site or the site does not seek involvement from the CTU. CTU involvement, where requested, can vary considerably, from engagement in the preparation activity to attendance at the inspection. Whether the CTU is present at the inspection or not, involvement in the preparation activity will ensure the site has the correct information and documentation for the dossier and for the inspection itself.

Top tips to ensure the inspection process runs as smoothly as possible:
- Establish roles and responsibilities of CTU and site staff and lines of communication.
- Seek engagement from the first notification of the inspection. Identify key person leading inspection preparation at site, usually in R&D and offer support.
- If possible, review sections of the dossier relevant to the trial to ensure the correct information has been submitted.
- Require that CTU trial team check that all site paperwork held at the CTU (including investigator site file, pharmacy site file, central monitoring requests/QC checks (e.g.,

accountability logs, delegation logs)) are up to date, and that they offer to help their site contact with any requests they may have.

- Consider undertaking an on-site monitoring visit to ensure:
  o the correct documentation is held in the site files (including pharmacy and other involved departments),
  o data have been reported appropriately,
  o supplies are managed appropriately,
  o any tissue samples are stored as required and
  o findings from any previous central or on-site monitoring visits have been resolved appropriately.

  An alternative approach may be to ask the site to notify the CTU of any gaps in the documentation they hold.

- Consider requesting to attend the inspection to help facilitate the process and answer any queries the site may have; permission will be at the sponsor/site's discretion.

- If not in attendance at the inspection, ensure the relevant CTU staff are available for the duration of the inspection to answer any queries the site may have or to forward any required documentation.

- If possible, review sections of the inspection dossier relevant to the trial to ensure the correct information is submitted.

- Work with the site to ensure any CAPAs are addressed appropriately and in a timely manner.

7.3 Where a laboratory providing services for a trial managed by the CTU is selected for GCP inspection.

Suggestions to help prepare a laboratory for a GCP inspection are described below, however, will also be applicable to other service/collaborative functions:

The Inspection Lead or delegate should meet with the laboratory research lead as soon as possible after the notification of inspection to determine the level of preparation required. Preparation for the inspection may then include the following:

- Confirmation of trials for which the laboratory is providing sample processing/analysis, ensuring that laboratory staff are aware that research samples are being handled and contracts/agreements are in place (depending on the relationship between the CTU/host organisation and laboratory).

- A review of trial documentation held at the laboratory (e.g., protocol, laboratory manual, training) to ensure this is current and can be made available for inspection.
- A review of sample tracking, from receipt (including trial sample labelling), processing/analysis, reporting (including procedures for reporting abnormal results urgently) and storage. This will help identify potential questions that may be raised by inspectors and any additional preparation that is required. For example:
  - What integrity checks are performed on the sample at receipt?
  - What evidence is there that the sample has been processed/analysed in accordance with the consent of the patient and the protocol?
  - What evidence is there to support the integrity of the laboratory result (e.g., QC and QA checks, equipment maintenance and training records, reports reviewed and released by qualified staff, evidence trail of sample storage and data)?

Direct access to laboratory systems and documentation (paper and electronic) may be required, therefore, consider how inspectors may access systems and files, particularly during a remote inspection.

The UKCRC Registered CTUs Network guidance documents on QA oversight of laboratories and self-assessment questionnaire can be used on an ongoing basis to maintain 'inspection readiness' and as useful prompts during the preparation of laboratories for inspection. These are available on the UKCRC Registered CTU Network website.

References

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 No. 1031 (as amended).
2. European Medicines Agency, Good Clinical Practice Inspectors Working Group Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) (2018)
3. MHRA website: https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

Additional Reading

- MHRA blog - GCP Inspections: Expectations and the do's and don'ts for hosting.
- MHRA blog - Inspectors grounded – a year of innovation.
- MHRA blog - MHRA Good Practice (GxP) Inspections during the COVID19 outbreak

- MHRA blog - MHRA planning for return to on-site (GxP) inspections.
- MHRA Inspection Metrics

Acknowledgements

This guidance document has been developed with the support of the following contributors:

Annex 1

Revision History

In response to COVID19 and the restrictions on travel and face to face contact, there was a change to the way of working for the inspectorate. Whilst the MHRA were already conducting some activities remotely pre-pandemic, most of their inspections were on-site. The pandemic and lockdown restrictions necessitated a shift to increased remote working, some aspects of which will continue post-pandemic.

In addition, the UK left the EU on 31 January 2020. Existing EU medicinal product legislation continued to apply in the UK during the Brexit transition period under the terms of the EU-UK Withdrawal Agreement. When that period expired on 31 December 2020, the UK left the single market and the customs union and became a "third country" with regard to the EU. At the expiry of the transition period, existing EU legislation was automatically incorporated into UK domestic legislation as far as possible. Any EU legislation that takes effect after the expiry of the transition period will not automatically apply in the UK.

From 1 January 2021, the MHRA will be the UK's standalone medicines and medical devices regulator. As a result of the Northern Ireland protocol, different rules will apply in Northern Ireland than in GB; broadly, Northern Ireland will continue to follow the EU regulatory regime, but its national competent authority will remain the MHRA.

New legislation in the UK will be given effect via the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019 (the "**Exit Regulations**").

This document, therefore, has been revised to include guidance for the preparation and conduct of remote inspections, updates to the MHRA's inspection reporting process and following the UK's exit from the EU.

Table of acronyms

Acronym	Description
CAPA	Corrective And Preventive Actions
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRO	Contract Research Organisation
CTU	Clinical Trials Unit
eTMF	Electronic Trial Master File
EU	European Union
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPvP	Good Pharmacovigilance Practice
HRA	Health Research Authority
ICH	International Council for Harmonisation
MHRA	Medicines and Healthcare products Regulatory Agency
SOP	Standard Operating Procedure
TMF	Trial Master File