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Preparing for Regulatory Inspections Standard Operating Procedure (SOP)

Introduction and Aim

This SOP describes the process for planning, hosting and managing regulatory inspections and external audits where a Cardiff Joint Research Office (JRO) organisation (either Cardiff and Vale Local University Health Board or Cardiff University) has been selected for a Sponsor or host site inspection. This SOP also details the process for responding to inspection findings.

Objectives

To explain the JRO processes for:

- responding to notifications of regulatory inspection;
- preparing for regulatory inspections;
- managing and hosting regulatory inspections;
- responding to findings from inspections,

of either Cardiff and Vale UHB (CAVUHB) or Cardiff University (CU) as a Sponsor organisation or host Site of clinical trials.

Scope

This SOP applies to the JRO's procedures for preparing for and managing regulatory inspections of CAVUHB and CU in relation to each organisation's involvement as a Sponsor and/or a Host Site of clinical research studies and trials. The SOP also applies in the event that CAVUHB and CU are jointly inspected in respect of clinical research study activity.

This SOP covers the JRO's processes for:

- planning, hosting and management of on-site and remote inspections);
- responding to inspection findings.

Types of regulatory inspections typically include, but are not limited to, all categories of inspections conducted by Competent Authorities such as:

- the Medicines and Healthcare products Regulatory Agency (MHRA);
- the US Food and Drug Administration (FDA);

for which a JRO organisation has received a Notification of Inspection.

This SOP largely details the procedures for managing a routine MHRA Statutory GCP inspection, but the principles outlined in the SOP may be applied to other types of regulatory inspection.

This SOP **does not apply to:**

- the procedures for Human Tissue Authority (HTA) inspections or audits associated with either organisation's compliance with the Human Tissue Act (HTA). Such inspections and audits are managed by the respective organisation's HTA Teams;
- the procedures for regulatory inspections of other Directorates or CU departments or services (although it is acknowledged that JRO staff may assist with the preparations for or response to findings arising from these inspections);
- the procedures for internal Sponsor audits led by either CAVUHB or CU (refer to the UHB SOP for Audits (Ref: 236);
- the procedures for internal audits of the JRO conducted by other departments within CAVUHB or CU;
- the procedures for financial audits.

Responsible Personnel:
The JRO Senior Management Team (SMT) is responsible for planning, hosting and managing regulatory inspections and for coordinating the response to any findings arising from inspections. The JRO Research Governance Team will assist the JRO SMT with inspection preparations and coordination. The involvement of other JRO Teams may be requested by JRO SMT.

In the case of inspections of either CAVUHB or CU as a Sponsor organisation, the respective organisation's JRO staff members will lead on undertaking the procedures outlined in the SOP, with support from the partner JRO organisation and other appropriate staff members from across both organisations (e.g. staff from the Cardiff Centre for Trials Research (CTR)).

The JRO Director is responsible for input into the inspection planning, the hosting of the inspection and for the review and authorisation of any inspection response prior to finalisation.

The JRO Research Governance Team is responsible for authoring, reviewing and updating this SOP. The JRO Quality Management Group is responsible for reviewing the SOP. The joint Clinical Trials Governance Group (CT-GG) and Joint Research Governance Group (JRGG) is responsible for approving the SOP.

Equality Health Impact Assessment	An Equality Health Impact Assessment has been completed on the Research Governance Policy and Procedure (UHB099) under which this procedure sits.

Documents to read alongside this Procedure	– Medicines for Human Use (Clinical Trials) Regulations (2004), as amended: The Medicines for Human Use (Clinical Trials) Regulations 2004 (legislation.gov.uk) – UK Policy Framework for Health and Social Care Research 2017 - https://www.hra.nhs.uk/planning-and-improving-researchliciesstandards-legislation/uk-policy-framework-health-social-careresearch/ – ICH Good Clinical Practice (GCP) E6(R2) (as amended)
Approved by	Joint Research Governance Group
Accountable Executive or Clinical Board Director	Medical Director
Author(s)	JRO Research Governance Team

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1.0	02/05/2025	31/07/2025	N/A, first version

Contents

1.0 DEFINITIONS/ABBREVIATIONS

ARSAC	Administration of Radioactive Substances Advisory Committee

C&C	Capacity and Capability
CAG	Confidentiality Advisory Group
CAVUHB	Cardiff and Vale University Health Board
CE	Conformité Européene (CE)
CI	Chief Investigator
CRO	Contract Research Organisation
CTIMP	Clinical Trials of Investigational Medicinal Products
CTR	Cardiff Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
CUBRIC	Cardiff University Brain Research Imaging Centre
DMP	Data Management Plan
EPR	Early Project Review
HCRW	Health and Care Research Wales
HRA	Health Research Authority
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
JRO	(Cardiff) Joint Research Office
MHRA	Medicines and Healthcare Products Regulatory Agency
mNCA	Model Non-commercial Clinical Trial Site Agreement
OBI	Office Based Inspection
OID	Organisation Information Document
PI	Principal Investigator
QMG	Quality Management Group
RAF	Risk Assessment Framework
REC	Research Ethics Committee
R&D	Research and Development
SAP	Sponsor Assessment Process
SOP	Standard Operational Procedure
SoE	Schedule of Events
SoECAT	Schedule of Events Cost Attribution Template
Sponsor	The individual, company, institution or organisation, which takes on the ultimate responsibility for the initiation, (management or arranging the initiation) of and/or financing (or arranging the financing) for that research
TMF	Trial Master File
UKCA	UK Conformity Assessment
UK-CRC	UK Clinical Research Collaboration

UKPF	UK Policy Framework for Health and Social Care Research 2017 (as amended)

2.0 GENERAL INFORMATION

Inspections and audits follow similar processes and both are intended as a way of evidencing and verifying that an organisation or department is operating in compliance with specific regulations, practices and/or professional standards. While inspections and audits are useful for highlighting episodes of poor practice and areas of risk, they also function to provide public assurance and act to identify better ways of working and opportunities for continuous improvement.

2.1 Inspections

In the context of clinical trials, an inspection is defined as: '*The act by a 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)'.* (International Conference on Harmonisation (ICH) Good Clinical Practice Glossary, Definition 1.29).

In the UK, the MHRA has rights conferred under the Regulations 325 and 327 of the Human Medicines Regulations 2012 (SI 2012/1916) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) to enter any premises involved in Clinical Trials of Investigational Medicinal Products (CTIMPs) and Clinical Trials of Medical Devices (Medical Device Trials) for the purposes of carrying out an inspection.

The MHRA Good Clinical Practice (GCP) Inspectorate is responsible for inspecting clinical trials to ensure compliance with GCP. The function of the GCP Inspectorate is to assess the compliance of organisations with UK and EU legislation relating to the conduct of Clinical Trials of Investigational Medicinal Products (CTIMPs).

Any Sponsor holding Clinical Trial Authorisations (CTA) from the MHRA, NHS organisations hosting a CTIMP or Medical Device Trial or any organisation providing clinical trial services to Sponsors (e.g. a laboratory or IT provider), may be subject to a GCP inspection at any point in the trial life-cycle (from study set-up to the point the trial is archived).

MHRA GCP inspections can be conducted on-site or remotely, or a combination of both.

Sponsor and host organisations may be inspected by other organisations such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The process detailed in this SOP largely focuses on preparing for MHRA GCP

Inspections, but the processes described should be adapted for any category of regulatory inspection, where Cardiff University or Cardiff and Vale UHB are selected for inspection either as a Sponsor or host (site) organisation.

3.0 PROCEDURES

3.1 PLANNING FOR REGULATORY INSPECTIONS

3.1.1 Categories of MHRA GCP inspections

The majority of MHRA GCP inspections are carried out under the MHRA's risk-based compliance programme. The MHRA uses available information to determine the risk category of an organisation (either as a Sponsor or a Host Site). This might be based on information from previous inspections (including inspections conducted by other regulatory bodies), organisational change or intelligence received from external sources. MHRA GCP Inspection metrics are made publicly available by the MHRA on its website.

GCP inspections are categorised as either systems-based or study-specific:

i. **Systems-based inspections:** focus on the clinical trial systems and procedures in place within an organisation (e.g. quality assurance or computer systems). Normally a number of clinical trials will be selected for scrutiny as part of a systems-based inspection;
ii. **Study-specific inspections:** assess specific clinical trials which have been completed and reported.

The MHRA may conduct the following types of GCP inspection:

i. **Routine requested inspection:** this is the most common category of GCP inspection. Routine GCP inspections are conducted as per the flowchart provided in Appendix 2. Organisations typically receive at least 3 months' notice of the MHRA's intention to conduct a routine inspection;
ii. **'For cause' or 'triggered' inspection:** a 'for cause' or 'triggered' inspection is normally initiated as a result of information received by the MHRA, usually relating to safety or an identified concern with a site or Sponsor organisation (e.g. a serious breach report). The MHRA is not required to provide any notice of a triggered or 'for cause' inspection and may arrive at an organisation unannounced, or provide limited notice of their intention to inspect.

Other types of inspection or audit will usually fall into one of the above categories (or as indicated by the regulatory agency or auditor).

3.1.2 Receiving notification of an inspection

Organisations typically receive around 3-6 months' notice of a planned inspection date.

In the case of routine requested GCP inspections of a Sponsor organisation, the MHRA will issue a preliminary notification of a statutory inspection to the Sponsor organisation via email. The notification is normally issued to the named Sponsor contact as contained in the MHRA's records. The JRO Research Governance Team is responsible for ensuring that the Sponsor contact details for Cardiff University and Cardiff and Vale UHB held by the MHRA are kept up to date and accurate.

The inspection notification will describe the required timelines for communication with the inspectorate and include a request for a completed MHRA *Inspection Dossier* (TPL/005/01) and *Clinical Trials Spreadsheet* (TPL/005/02) to be provided to the MHRA within 30 calendar days of receipt of the notification (see section 3.2.2 regarding the completion of the Pre-Inspection Dossier).

In the case of routine requested GCP inspections of CAVUHB as a Host organisation, the Sponsor of the trial concerned will normally notify the Principal Investigator (PI) and the CAVUHB R&D Office. In the event that the Sponsor does not notify the R&D Office directly, the PI (or their delegate) should notify the CAVUHB R&D Office as soon as they receive the notification from the external Sponsor.

Depending on which JRO organisation is being inspected, the following role holders (or their appointed deputies) will act as the Lead JRO contact for liaison and correspondence with the Lead Inspector/Auditor in the lead-up to the inspection date:

Table 1: JRO Inspection Lead

Sponsor organisation	**Nominated JRO Lead for liaison with a Lead Inspector**
Cardiff University	Head of Research Integrity, Governance and Ethics (RIGE)
Cardiff and Vale University Health Board	CAVUHB Research and Development Manager

3.1.3 Allocating JRO staff resource in the event of an inspection

As soon as possible following the receipt of a notification of inspection, the JRO Director shall consult with the JRO SMT, to determine the levels of staff resource available and shall allocate JRO staff members to lead on specific inspection preparation tasks and areas of activity. Staff members from all JRO teams may be requested to assist with areas of inspection preparedness. Requests for staff time will be made in consultation with the respective team lead or line manager.

The JRO Director may choose to convene an Inspection Support Working Group consisting of relevant JRO staff and other key staff from across CAVUHB and/or CU (e.g. CTR representatives), as deemed appropriate.

3.2 Planning for a Sponsor Inspection

3.2.1 Responding to a notification of inspection and notifying the relevant individuals

In the case of MHRA inspections, upon receiving notification of a regulatory inspection of a Sponsor organisation, the relevant Sponsor representative will notify the following individuals, within 24 hours (or as soon as is practical):

- the Director of the JRO;
- the CU Head of Research Integrity, Governance and Ethics (RIGE)/the CAVUHB Research and Development Manager (depending on which organisation has received the notification);
- Other members of the JRO SMT as appropriate.

The JRO Director (or their delegate, e.g. a member of the JRO SMT) is responsible for issuing a formal acknowledgement and response to the notification of an MHRA regulatory inspection, within 10 calendar days of its receipt.

The JRO Director and JRO SMT members will then agree which individuals within their respective organisations need to be notified of the inspection notification prior to the Pre-Inspection dossier being submitted to the MHRA. This list may include the following individuals (and/or others as determined by the JRO Director):

- The Director of Research Delivery, CAVUHB;
- The CAVUHB Medical Director (NB. this is mandatory where CAVUHB is selected for a Sponsor inspection, but may be determined by JRO SMT for inspections of CU);
- The Director of Cardiff University (CU) Research Services (NB. this is mandatory where Cardiff University is selected for a Sponsor inspection. This notification is optional for CAVUHB Sponsor inspections);
- The CU Pro-Vice Chancellor for Research and Innovation (NB. this individual is also the Chair of the CU Open Research, Integrity and Ethics Committee);
- The Pro-Vice Chancellor for the CU College of Biomedical and Life Sciences (BLS);
- The CU Dean of Research for the College of BLS;
- Relevant Heads of Schools within the CU College of BLS, such as the Head of the Schools of Medicine, Dentistry, Optometry and Vision Sciences, Pharmacy and Pharmaceutical Sciences (to be determined based on levels of

regulated trial activity within the School. NB. this is mandatory where Cardiff University is selected for a Sponsor inspection. This notification is optional for CAVUHB Sponsor inspections);

- The Directors of the Cardiff Centre for Trials Research (CTR);
- The Head of Quality Assurance and Regulatory Affairs, CTR;
- The Chair of the joint Clinical Trials Governance Group (CT-GG);
- Other key CU and CAVUHB departments/staff members as appropriate and as determined by JRO SMT. This may include, but is not limited to, any or all of the following:
    - the CAVUHB Clinical Research Facility (CRF);
    - the R&D Leads of each CAVUHB Clinical Board;
    - Pharmacy;
    - Relevant Support Departments
    - NHS and/or University IT;
    - Information Governance and Data Protection personnel;
    - Human Tissue Act (HTA) compliance staff;
    - Risk and Compliance departments;
    - central audit and quality improvement functions;
    - Finance (to notify regarding any inspection fees and likely invoices);
    - NHS Clinical Engineering or relevant University equivalent department (e.g. CUBRIC) responsible for maintenance or calibration of devices and equipment used in regulated trials or studies;
    - Estates.

3.2.2 Inspection/ Preparation Period- Stage 1 (Completion of the MHRA Pre-Inspection Dossier and Clinical Trials Spreadsheet)

In the case of routine risk-based MHRA inspections of a Sponsor organisation, the MHRA will request that a Pre-Inspection Dossier and Clinical Trials Spreadsheet are completed and returned to the MHRA within 30 days of the date of the notification of inspection. Submission of the Pre-Inspection Dossier and Clinical Trials Spreadsheet must be completed within 30 days of receiving the notification of inspection. This date should be communicated to all relevant staff.

The respective JRO Inspection Lead will lead the coordination of the Pre-Inspection Dossier and will agree an internal deadline for the completion of the Pre-Inspection Dossier and Checklist, ahead of the 30 day deadline.

The JRO Research Governance Teams are responsible for maintaining a template MHRA Inspection Dossier and Clinical Trials Spreadsheet on behalf of both CU and CAVUHB as part of its routine inspection readiness preparations. These templates will be routinely reviewed (at least on an annual basis) to ensure they are kept up to

date, with any updates and changes reported to the JRO Quality Management Group (QMG).

The respective Sponsor organisation staff within the JRO Research Governance Team are responsible for completing the Pre-Inspection Dossier and Clinical Trials Spreadsheet, with oversight provided by the relevant JRO Inspection Lead. Within two working days of receiving a notification of inspection, the relevant Research Governance Team will review the template Pre-Inspection Dossier and Clinical Trials Spreadsheet and will commence the process of updating it ready for submission to the MHRA..

Further input into sections of the Pre-Inspection Dossier and Clinical Trial Spreadsheet may be sought from relevant individuals and groups as determined by JRO SMT. This may include but is not limited to: the Cardiff Centre for Trials Research (CTR), Pharmacy departments, laboratories, IT and Information Governance, Trial Managers and CIs and external Clinical Trials Units (CTUs) and service providers. The relevant teams and departments will be referenced on the template Pre-Inspection Dossier and should be contacted as early on in the process as possible and informed of any internal deadlines for completion.

The JRO Director and relevant members of JRO SMT will provide a final quality control (QC) review of the Pre-Inspection Dossier, before it is submitted to the MHRA. The MHRA Inspectorate can be contacted with any questions about the completion of the Dossier. A GCP Inspection Dossier Checklist should be completed before the Dossier and Clinical Trial Spreadsheet are finalised. Approval of the final version of the Pre-Inspection Dossier and Clinical Trials Spreadsheet must be sought from the JRO Director prior to submission to the MHRA.

In the case of inspections by other regulatory bodies, the pre-inspection instructions and requirements as provided by the regulator should be adhered to. The individuals and teams listed in Section 3.2.4 will be responsible for any pre-inspection actions.

Prior to the submission of the Pre-Inspection Dossier, the JRO Inspection Lead will develop a JRO Inspection Communication Plan, using TPL/005/03. The purpose of this document is to keep relevant individuals, teams and committees within the JRO and across both CU and CAVUHB up to date on the inspection preparations at all stages. The Communication Plan may be adapted according to the type of inspection.

In accordance with the Communication Plan, formal communication should be prepared by the relevant JRO Research Governance Team, in collaboration with the JRO SMT, to notify the following individuals that the JRO organisation has received a notification of inspection and that a Pre-Inspection Dossier has been prepared:

- all staff listed as Chief Investigators (CIs) and/or Co-CIs of the organisation's Sponsored CTIMPs or Medical Device Trials;
- Directors of any Clinical Trials Units (CTUs) appointed to work on a CU or CAVUHB Sponsored trial);
- all Senior Trial Managers and Trial Managers working on the respective organisation's Sponsored CTIMPs or Medical Device Trials (the Sponsor organisation may delegate this communication to the appointed CTU);
- Trial Managers will be asked to notify all site PIs working on CU or CAVUHB Sponsored trials of the forthcoming inspection. PIs should be notified that their site may be selected for inspection as part of the Sponsor inspection and that confirmation will be provided as soon as more information becomes available;
- where the inspection is an inspection of CAVUHB as a Host Site: all PIs listed on the Clinical Trials Spreadsheet;
- in the case of multi-centred trials, the R&D Department of any NHS organisation acting as a Host Site in the trial.

At this stage, the JRO should make it clear that: the trials to be selected for inspection are not yet known; no date has been set for the inspection and that further information will be made available in due course.

3.2.3 Stage 2 of the Inspection Preparation Period- following submission of the Pre-Inspection Dossier

While awaiting a response from the regulatory body, members of the relevant JRO Research Governance Team should commence the following areas of activity and associated tasks (Stage 2 of the Inspection Preparation Period):

- convene an Inspection Working Group consisting of relevant members of staff (as agreed by the JRO Inspection Lead). The Inspection Working Group should remain in place for the duration of the inspection and to oversee the JRO's response to any inspection findings;
- prepare a JRO Inspection Risk Assessment to document study-specific and JRO-level risks (based on the JRO Risk Register). The Risk Assessment and progression of subsequent mitigation strategies will be overseen by the Inspection Working Group;
- consider any inspection training requirements and develop a training programme for study management teams, CIs and PIs;
- consider any logistical and practical aspects of hosting an inspection (see section 3.2.4 ii);
- ensure all relevant JRO staff have up to date GCP training and an up to date brief CV in place;

- remind CTUs to ensure that all staff working on trials Sponsored by the relevant JRO organisation have up to date GCP training and an up to date brief CV in place;
- remind CIs working on trials Sponsored by the relevant JRO organisation to update their GCP training and brief CV if needed;
- remind all CTUs to review the Trial Master File(s)* (TMFs) held for trials Sponsored by the relevant JRO organisation to ensure these are up to date (the CTU may opt to arrange an internal peer reviews of their TMFs at this point);
- request that all site PIs review their Investigator Site Files (ISFs) to ensure these are up to date;
- commence a review of the Sponsor TMF and ensure all sections are up to date;
- ensure all JRO staff are trained in and familiar with relevant JRO SOPs, guidance and key CU/CAVUHB organisation-level policies and procedures;
- request that CTUs ensure that their staff are trained in and familiar with all relevant CTU SOPs, guidance and relevant organisation-level policies and procedures;
- ensure that CIs are made aware of and are familiar with relevant JRO and CTU SOPs, guidance and key CU/CAVUHB organisation-level policies and procedures (where applicable to their role).

*****a TMF review involves ensuring that all essential and relevant supplementary documentation is available on the TMF and adding file notes where necessary to explain the location of a document or to explain any gaps in the TMF.

3.2.4 Inspection Preparation Stage 3: Confirming the date and arrangements for an inspection and provision of the Inspection Plan

In the case of a routine risk-based MHRA inspection, the MHRA will confirm an inspection date following receipt and review of the Pre-Inspection Dossier. This may be 3-6 months after the submission of the Pre-Inspection Dossier, or later, depending the availability of Inspectors.

The MHRA will provide an Inspection Plan ahead of the inspection, usually following consultation with the JRO Inspection Lead.

The JRO Inspection Lead should then:

i. in the case of an MHRA inspection- liaise with the Chair of the joint Clinical Trials Governance Group (CT-GG) to determine whether more frequent CT-GG meetings are required in the period leading up to the inspection. The CT-

GG Chair may determine that specific Task and Finish Groups are established to support the JRO in its inspection preparations;

ii. identify a suitable space and location for an on-site inspection or audit to be held. The JRO Inspection Lead should consult with the JRO Director to identify a suitable space for the inspection (this may be in the JRO offices or another suitable CAVUHB or CU space). This should normally include a main inspection room for the inspection team, with enough space for document review and adequate IT facilities/internet connection. Further smaller rooms or 'breakout spaces' may need to be identified and reserved for interviews. The JRO Inspection Lead and nominated JRO staff will need to be available and in close proximity to the inspection room(s) to respond quickly to any requests for information or documents. It is recommended that a 'Control Room' is identified for JRO staff to occupy during the inspection, in order to coordinate requests from the Inspector(s).

In the case of all other types of inspection, the JRO Research Governance team shall be responsible for preparing the necessary paperwork as requested by the regulator , in consultation with the JRO Inspection Lead. The steps outlined in sections 3.2.1-3.2.3 should be followed, in line with the requirements of the regulatory body and in discussion with JRO SMT.

As soon as the Inspection Plan is issued, the JRO Inspection lead (or their delegate) will notify:

- the CIs, Trial Managers and site PIs working on all of the trials selected for TMF review and request that they keep the dates of the inspection free from other commitments, in the event that they are required to be interviewed by the MHRA Inspector (see section 3.2.6).
- any IMP Manufacturers of IMPs used in the selected trials;
- any Clinical Research Organisations (CROs) involved in the selected trials;
- any other organisations as required contractually.

Details of the inspection team, duration of the inspection, any logistical information and the estimated fees associated with the inspection will normally be communicated by the MHRA at this point.

When the date of the inspection is known, the JRO Inspection Lead (or their delegate) should:

- inform the JRO Director and the JRO SMT of the date and details of the inspection before notifying the teams and individuals listed in section 3.2.1 of this SOP. The JRO Inspection Lead should liaise with the JRO Director to establish the levels of JRO staff availability for the duration of the inspection. Consideration should be given to periods where high levels of annual leave or organisation-wide closure are likely (e.g. the school summer holidays or

Christmas period). Liaison with the MHRA regarding flexibility on inspection dates may be necessary and should be facilitated by the JRO Inspection Lead in agreement with the JRO Director;

- liaise with the JRO Director, JRO SMT and the relevant CU or CAVUHB budget holder to notify the relevant Finance Department. In the case of MHRA inspections, up to date information on inspection fees may be found here;
- ensure all necessary rooms are booked for inspection use on the required dates;
- draft an inspection rota assigning appropriate JRO staff to act as inspection interview scribes (to take notes during interviews) and at least two 'Control Room' staff to be available at all times to log and respond to document requests from Inspectors during the inspections;
- ensure that all required JRO staff members are aware of the inspection dates and are requested not to book non-essential annual leave during this time (where possible);
- arrange any catering and refreshments required for inspectors (where required).

The MHRA Inspection Plan will normally identify a number of Trial Master Files (TMFs) for review. The Inspection Plan may also identify any trial systems that the MHRA may wish to focus on during the inspection (e.g. Pharmacovigilance/safety reporting, IT, data management etc.).

Note: This does not mean that the inspection will be limited to those selected trials or systems only. The MHRA reserves the right to request access to any TMFs during the inspection, regardless of whether the trial is selected for inspection. Inspectors are not obliged to follow the Inspection Plan and may choose to review other areas when they commence the inspection.

Note: the MHRA may determine that an Office Based Inspection (OBI) is necessary prior to the on-site inspection. An OBI involves a video call with the MHRA ahead of the on-site inspection and the MHRA may request that certain documentation is provided for review at this stage. If an OBI is deemed necessary this will be detailed on the Inspection Plan. OBIs are intended to ensure that the on-site inspection is efficient.

For other types of inspection, confirmation of the date and logistics should be managed in accordance with the instructions provided by the regulator.. The principles outlined in section 3.2.4 may be adapted for other regulatory inspections..

3.2.5 Clinical Trials selected for TMF Review

The MHRA Inspection Plan will identify a number of trials from the Clinical Trial Spreadsheet provided as part of the Pre-Inspection Dossier. The MHRA will request

that the selected trial TMFs are made available during the inspection. As soon as the selected trials are made known by the MHRA, the relevant JRO Research Governance Team (under the leadership of the JRO Inspection Lead) should liaise with the relevant Trial Manager(s) and CI to:

- notify all staff working on the trial (CTU and host trial site staff) that the trial has been selected for an MHRA GCP Sponsor inspection;
- request that they keep the inspection dates free, as they are likely to interviewed as part of the inspection (remote interviews may be arranged if there is an unavoidable schedule conflict);
- verify that the CTU has reviewed their TMF to ensure this is up to date (the CTU may opt to arrange an internal peer review of the TMF). A representative of the Sponsor may assist with this process where required (see section 3.2.3);
- verify that all site PIs have reviewed their Investigator Site Files (ISFs) to ensure this is up to date (see section 3.2.3);
- undertake a final review of the Sponsor TMF (for CU Sponsored trials) and ensure all sections are up to date;
- arrange a meeting with the CI and Trial Manager(s) to ensure they are aware of the inspection and to prepare them for a potential MHRA Inspector interview (see *JRO information Sheet for MHRA Inspection Preparation-Training Document [IS/005/01]).*
- where CAVUHB is a trial site or in the case of inspections of CAVUHB as a host site, medical record access will need to be arranged for Inspectors. The JRO Inspection Lead should alert the relevant medical records department and complete any access requirements;
- request that all staff working on the trial and Trial Management Group (TMG) members have up to date GCP training and a brief CV in place (and that copies of these are available within the CTU);
- ensure that all Sponsor, CTU and Host Site staff working on the trial are familiar with key SOPs and trial processes and refresh any training where necessary. Staff working on the trial should be encouraged to raise any questions or highlight any gaps in their knowledge with the Sponsor and CTU as early as possible;
- establish whether any electronic or remote access is required for Inspectors to have access to the TMFs. Liaison with the CAVUHB or CU IT departments will normally be necessary to facilitate read-only access to electronic systems and audit trails, ahead of the inspection or audit.

As soon as the Inspection Plan is confirmed, the JRO Inspection Lead will notify the CI and Trial Manager(s) and any other key trial staff (e.g. Data Managers, Statisticians and/or trial site staff) of the dates and timings of any Inspector interviews and request that they commence a final TMF review.

The TMF(s) will need to be made available to the inspector(s)/auditors during the inspection or audit. If electronic TMFs (eTMFs) are used, then full access will need to arranged for the inspector/ in time for the inspection. The JRO Senior Management Team and the relevant JRO Research Governance Team should ensure that any necessary IT access is facilitated ahead of the inspection.. The method for document requests should be agreed with the Lead Inspector ahead of the inspection.

The JRO Inspection Lead should identify appropriate JRO staff members to be available during the inspection

3.2.6 Individuals identified for interviews

The MHRA Inspection Plan will list members of staff identified for an interview with the MHRA Inspectors. Any member of the organisation's staff can be identified for an interview with the MHRA Inspector during the inspection. The interview schedule will be made known to the organisation as part of the Inspection Plan, but inspectors reserve the right to request an unscheduled interview with any team or member of staff during the inspection, as they deem appropriate.

The JRO Inspection Lead (or their delegate) is responsible for ensuring all JRO staff are aware of their responsibilities during the conduct of the inspection (e.g. interview times, tasks associated with supporting the inspection and the location and availability of essential documentation).

The JRO Inspection Lead (or their delegate) will notify individuals of the dates and times of their interviews as soon as this is confirmed by the MHRA. The relevant JRO Research Governance team will arrange MHRA interview preparation training with the members of staff concerned, in line with the JRO *Guidance for MHRA Inspection Preparation- Training Document* (**ref).**

The JRO Inspection Lead (or their delegate) will inform staff selected for an inspection interview that they should be ready to:

- explain about their professional background (e.g. education, clinical and research training (including GCP)) and experience;
- explain their role in the trial (e.g. CI, PI, Trial Manager, Sponsor representative, Data Manager etc.)
- explain or answer questions about the trial design and implementation at sites;
- describe any SOPs, policies and procedures which govern their work and role in the trial;
- provide documentation relating to trial actions and activities, if requested to do so;

- explain an ‘end-to-end’ trial process or system (for which they are responsible) in detail and evidence that they understand how to operate in compliance with GCP.

3.3 Planning for a CAVUHB Host Site Inspection

CAVUHB may be notified of an inspection for a hosted study as part of an external Sponsor inspection. In this instance, the CAV Research Governance Team (under the leadership of the R&D Manager) should liaise with the relevant Sponsor Trial Manager and CI/PI to:

- notify all staff working on the trial and applicable support departments at CAVUHB that the trial has been selected for an inspection
- request that they keep the inspection dates free, as they may be interviewed as part of the inspection (remote interviews may be arranged if there is an unavoidable schedule conflict);
- verify that site PI(s) have reviewed their Investigator Site Files (ISFs) to ensure this is up to date (see section 3.2.3);
- arrange a meeting with the CI/PI and to ensure they are aware of the inspection and to prepare them for a potential MHRA Inspector interview (see *JRO Guidance for MHRA Inspection Preparation- Training Document* (**ref).**
- medical record access will need to be arranged for Inspectors. The JRO Inspection Lead should alert the medical records department and complete any access requirements;
- establish whether any electronic or remote access is required for Inspectors to have access to EHRs. Liaison with the CAVUHB IT departments will normally be necessary to facilitate read-only access to electronic systems and audit trails, ahead of the inspection or audit.
- request that all staff working on the trial have up to date GCP training and a brief CV is in place which are available within the ISF;
- ensure that all staff working on the trial are familiar with key SOPs and trial processes and the CI/PI should refresh any training where necessary. Staff working on the trial should be encouraged to raise any questions or highlight any gaps in their knowledge with CAVUHB RGT as early as possible;

As soon as the Inspection Plan is confirmed, the JRO Inspection Lead will notify the key trial staff of the dates and timings of any Inspector interviews and request that they commence a final ISF review.

The ISF will need to be made available to the inspector during the inspection. If electronic EHRs are used, then access will need to arranged for the inspectors in time for the inspection. The CAVUHB Research Governance Team should ensure that any necessary IT access is facilitated ahead of the inspection.. The method for

document requests should be agreed with the Lead Inspector ahead of the inspection.

The R&D manager should identify appropriate JRO staff members to be available during the inspection

Individuals identified for interviews

The MHRA Inspection Plan will list members of staff identified for an interview with the MHRA Inspectors. Any member of the organisation's staff can be identified for an interview with the MHRA Inspector during the inspection. The interview schedule will be made known to the organisation as part of the Inspection Plan, but inspectors reserve the right to request an unscheduled interview with any team or member of staff during the inspection, as they deem appropriate.

The JRO Inspection Lead (or their delegate) is responsible for ensuring all JRO staff are aware of their responsibilities during the conduct of the inspection (e.g. interview times, tasks associated with supporting the inspection and the location and availability of essential documentation).

The JRO Inspection Lead (or their delegate) will notify individuals of the dates and times of their interviews as soon as this is confirmed by the MHRA. The CAVUHB Research Governance team will arrange MHRA interview preparation training with the members of staff concerned, in line with the JRO *Information Sheet for MHRA Inspection Preparation- Training Document* (IS/005/01).

The JRO Inspection Lead (or their delegate) will inform staff selected for an inspection interview that they should be ready to:

- explain about their professional background (e.g. education, clinical and research training (including GCP)) and experience;
- explain their role in the trial (e.g. CI, PI, research nurse, pharmacist, etc.)
- describe any SOPs, policies and procedures which govern their work and role in the trial;
- provide documentation relating to trial actions and activities, if requested to do so;
- explain an 'end-to-end' trial process or system (for which they are responsible) in detail and evidence that they understand how to operate in compliance with GCP.

3.4 HOSTING AN ON-SITE REGULATORY INSPECTION OF CAVUHB or CU AS SPONSOR

3.4.1 Opening Meeting

In the case of MHRA inspections, the Lead Inspector will conduct an Opening Meeting at the first day of the inspection. The Opening Meeting will cover the legal basis of the inspection, any inspection logistics and brief introductions. The inspection host is expected to provide an introduction to the organisations. For Sponsor inspections of either CAVUHB or CU, the JRO Director (or their nominee) will deliver this introduction at the Opening Meeting. The introduction should be brief and focused on clinical trials.

The JRO should invite the CAVUHB and CU staff members listed in section 3.2.1 of this SOP to attend both the Inspection Opening and Closing Meetings, in addition to all CIs and Trial Managers of the trials selected for inspection. The JRO Director may determine that other staff members are invited as appropriate.

3.4.2 During the Inspection- document review and requests for evidence

In the case of a routine GCP Inspection, the inspection will largely focus on the examination of essential documentation and/or certain systems and processes (e.g. Computer System Validation). The JRO Inspection Lead will have liaised with the Lead Inspector ahead of the inspection to determine the format of the provision of documentation (e.g. paper and/or electronic) and a process for requesting any additional documents. The JRO Inspection Lead will agree a rota with relevant JRO staff to ensure that adequate staff are available throughout the duration of the inspection or audit and are on hand to provide documentation or information at short notice, as requested by the Inspectors..

Note: providing complete sets of essential documentation and details of systems is the method by which an organisation demonstrates its compliance with GCP.

Original documents should be provided to Inspectors (not duplicates, redacted or incomplete responses). If a document is missing, not available or will take a significant amount of time to retrieve, this should be disclosed to the Inspector(s) straight away. Further clarity can be sought from an Inspector if a request is not clear.

As part of an MHRA inspection, the inspector may visit other areas of the organisation, including pharmacy, archive facilities , CTUs and laboratories.

3.4.3 During an inspection- interviews

Staff members selected for interview with the MHRA inspector will be listed in the Inspection Plan and will usually include CIs, PIs and Trial Managers, but may also be extended to include staff from the organisation's senior management or executive board, IT and information governance/data protection departments, Pharmacy, laboratories, data management services, records managements and archives or clinical engineering/equipment maintenance. Ad-hoc question sessions may also be requested by the Inspector(s) during the inspection.

Interviews may take place in person or via an online platform (e.g. MS Teams).

Refer to the *JRO Information Sheet for MHRA Inspection Preparation- Training Document (IS/005/01)* for details on how to respond to an Inspector's interview questions.

Note: potential inspection findings and concerns will normally be flagged with the organisation as the inspection progresses, to ensure that the organisation has the opportunity to respond and provide any further clarification ahead of a finding being confirmed.

3.4.5 Inspection Findings

In the case of an MHRA inspection, the following gradings of findings may be applied:

- **Critical**
- Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that:
- the rights, safety or well-being of trial subjects either has been or has significant potential to be jeopardised, and/or
- the clinical trial data are unreliable and/or
- there are a number of Major non-compliances (defined in (d) and (e)) 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 (defined in (d) and (e))
- Where provision of the TMF does not comply with Regulation 31A 1-3, 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:**
  - 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
  - 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 good clinical practice has occurred, but it is neither Critical nor Major.

Any Critical findings in an MHRA GCP Inspection will be referred to the GCP Inspection Action Group (IAG). The IAG is multi-disciplinary group appointed to oversee all Critical inspection findings and determine any actions to be taken in addition to the review of the CAPA for the Critical finding(s). These might include onward referral to other agencies/regulators such as the General Medical Council (GMC) or Health Research Authority (HRA) or actions such as the suspension of any Clinical Trial Authorisations (CTAs), or prosecution of individuals.

In the case of other types of inspections, similar categories of gradings or levels of assurance (e.g. ‘Limited Assurance’, ‘No assurance’, ‘Full assurance’) may be applied.

3.4.6 Closing meeting

In the case of an MHRA Inspection, a Closing Meeting will be scheduled on the final day of the inspection. The JRO Director shall determine who is invited to attend the Closing Meeting, but this will normally include individuals listed in section 3.2.1 of this SOP.

The Inspector(s) will provide a summary of the inspection and a brief description of the inspection findings at the meeting, but the findings will not be confirmed until the Final Inspection Report is issued by the MHRA. The Inspector(s) may determine that follow-on inspections are required as part of the overall inspection (e.g. inspections of investigator sites in the case of Sponsor inspections).

Following the Closing Meeting, a confidential summary should be provided to the individuals listed in section 3.2.1 of this SOP, confirming the conclusion of the inspection and highlighting any key findings and information of relevance to the

organisation (but with the caveat that findings will be confirmed upon receipt of the Inspection Report).

Following the inspection, the MHRA will prepare and issue the organisation with a formal Inspection Report.

In the case of other types of inspection, a similar close-down/wrap-up meeting is usually convened to summarise findings, ahead of a formal report being prepared and issued.

3.5 RESPONDING TO AN INSPECTION (FOLLOW UP)

3.5.1 Receiving the Inspection Report

In the case of MHRA inspections, the MHRA Inspectorate will email the Inspection Report to the organisation's nominated contact. The timelines for the issuing of the Inspection Report may vary depending on the MHRA's workload and availability. The JRO Inspection Lead (or their delegate) is responsible for coordinating the formal response to the Inspection Report in the form of a corrective action and preventative action (CAPA) plan and will assign staff to lead on areas of the CAPA Plan as appropriate (following consultation with the JRO Director). Occasionally, periodic updates on the progress of proposed CAPA actions may be requested by the MHRA. The Lead Inspector may ask the organisation to provide additional clarification to any responses provided.

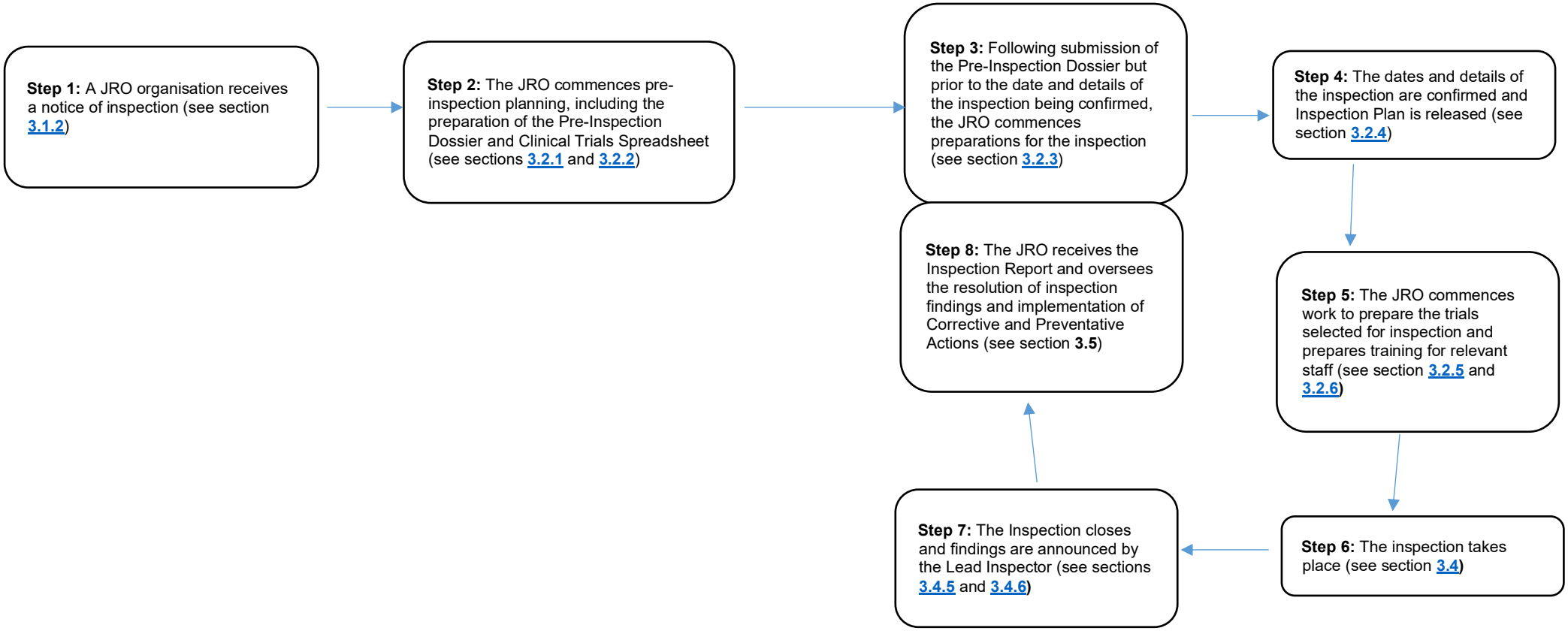
The JRO Inspection Lead should consult with the JRO Director to establish which individuals within CU and/or CAVUHB should be provided with a copy of the final Inspection Report and CAPA Plan. This may include individuals listed in section 3.2.1

The JRO Inspection Lead should present an overview of the Inspection Report to the CT-GG and the Inspection Working Group and should seek input on the CAPA Plan from members of the CT-GG where appropriate. The Chair of CT-GG may determine that inspection findings and actions should be escalated to other relevant CU and CAVUHB committees and senior management. The Inspection Working Group shall oversee the progress and closure of inspection findings and associated CAPAs.

When the MHRA deems that adequate responses have been received, a GCP inspection statement will be issued by email. The inspection statement should be shared with the JRO Director.

In the case of other types of inspection, an initial report is normally provided following the inspection and should be managed by the JRO in the same manner as an MHRA Inspection Report.

Appendix 1: SOP Flowchart: Preparing for an inspection or audit



Appendix 2: MHRA GCP Inspection Process Overview