Research Road Map

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Background: Clinical Trial Inspections

Health Canada (HC) has the authority to audit and/or inspect research sites conducting HC–approved clinical trials. The United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) also have the authority to audit and/or inspect Canadian research sites conducting FDA/EMA-approved clinical trials.

Sponsors, contract research organizations (CROs), funding entities, research ethics boards (REBs) and/or other bodies authorized by regulations and/or agreements with research sites may also have the authority to audit and/or inspect research sites.

The purpose of this roadmap is to help researchers prepare for these audits or inspections of clinical trials and to understand the audit/inspection process.

Definitions

Audit – an examination, verification or review of all activities, documents, facilities, equipment, records, and other resources associated with clinical research, including clinical trials, to determine whether all research activities were conducted in compliance with the study protocol, site-specific and/or sponsor-specific SOPs, institutional and REB policies, good clinical practice (GCP), and other applicable regulatory requirements and guidelines. Audits are typically conducted to help ensure compliance with applicable standards, to correct errors before the research is completed, to identify low or high rate of adverse events when research sites are compared, and to verify that the data is accurate and of quality.

Inspection - an official examination by regulatory authorities (e.g. HC or FDA) of all activities, documents, facilities, equipment, records, and other resources deemed by the regulatory authorities to be relevant and related to the clinical research, including clinical trials, to determine whether all research activities were conducted in compliance with the study protocol, site-specific and/or sponsor-specific SOPs, institutional and REB policies, good clinical practice (GCP), and other applicable regulatory requirements and guidelines. Inspection typically occurs at the research sites; however, inspection can also occur at the sites of the Sponsor, CRO, funding entities, REB and/or other locations deemed appropriate by the regulatory authorities. Following an inspection, an official written report is provided that lists all observations, deviations, and deficiencies noted during the inspection.

Purpose of Inspections

The main objectives of inspections of clinical trials involving human participants is to ensure that sponsors and investigators conduct clinical trials in accordance with Good Clinical Practices (GCP) as described by the International Conference on Harmonization (ICH) Guidance document E6 (R2) adopted by Health Canada, Food and Drug Administration (FDA) and European Medicines Agency (EMA). In Canada, clinical trials involving drugs with human participants must adhere to Part C, Division 5 of the Food and Drug Regulations. For details of the requirements, please refer to Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical Trials Involving Human Subjects" GUI-0100.

Tri council Policy statement (TCPS2 2018) also applies to clinical trials conducted in Canada. Clinical trials conducted under an IND or funded by the National Institutes of Health (NIH) must also adhere to the US Food and Drug Administration, Code of Federal Regulations, Title 21. Please refer here for details of the requirements.

The conduct of clinical trials in the European Union (EU) is governed by the Clinical Trials Regulation. Its aim is to ensure a greater level of harmonization of the rules of conducting clinical trials throughout the EU.

Inspections may be conducted at the facilities of the Sponsors, Qualified Investigators (clinical trial sites), Sponsor-Investigators, Research Ethics Boards, and Contract Research Organizations. Inspections can also be conducted at facilities of Site Management Organizations, Testing Laboratories, and any other sites conducting tasks under the scope of a clinical trial subjected to applicable regulations. Most inspections will be announced in advance. Notification is usually sent to the Sponsor and the site a minimum of 5 days and up to 4 weeks before the inspection is conducted. Inspections may also be conducted unannounced at the discretion of Health Canada, FDA or EMA. The inspection notice may indicate the purpose.

Examples of areas which may be involved in the inspection are:

- Study Regulatory Documentation- e.g. Health Canada Authorization, Research Ethics Board (REB) approvals, amendments
- Education, training and experience of all key research personnel- review of Task Delegation Log, CVs, Training Logs, and proper oversight by the Principal Investigator
- Adherence to the study protocol, deviation reporting
- Adherence to any written Standard Operating Procedures (SOPs), including N2 and/or study-specific working procedures
- Record Management
- Investigational Product (IP) Management
- Study Equipment Maintenance and Calibration
- Study Biological Specimens Handling
- Study Monitoring of the site by the Sponsor
- Drug Labeling
- Serious Unexpected Adverse Drug Reaction Reporting

The information contained in all documents should be complete, up-to-date, and in agreement with the raw data or source documents. Retrospective entries or

corrections should be dated and signed by the relevant individuals. The reason for late entries should be documented.

QI Responsibilities

Once informed of an upcoming inspection, the Qualified Investigator (QI) should inform all relevant areas/individuals, including but not limited to,

- Queen's HSREB, as per SOP 901.001External Audits or Inspections;
- KHSC VP, Health Sciences Research, as per policy 11-150 Health Research;
- All relevant personnel who have been involved in the study, including sub-investigators and study coordinators;
- All relevant hospital departments, e.g. Protection Services, Medical Records, Pharmacy, Core Laboratory, Clinical Engineering, Imaging, and clinical departments where the study visits took place.

If the inspection involves a clinical trial conducted in the WJ Henderson Centre for Patient Oriented Research (WJHCPOR), the QI has a responsibility to notify the KGHRI as per SOP-EAI-01 External Audits and Inspections. The designated KGHRI staff member will work with the QI and project team throughout the inspection cycle.

The QI and project team should ensure that original documents, including but not limited to the following, are available as applicable:

- Essential documentation (regulatory binder),
- Case Report Forms (CRFs),
- Informed Consent Forms (ICFs) for all research participants,
- Medical records/files and other source documents,
- Pharmacy records/files (management of investigational products),
- Other documents related to the study.

Access to medical records/files for the inspector(s) should be arranged in advance as per the KGHRI Accessing Medical Records for Research roadmap.

Inspection Visit, Exit Notice and Follow-up

The inspection visit usually takes approximately 5 days or longer if necessary. During the inspection visit, the Inspector(s) will conduct interviews with research personnel and review regulatory and study documentation. Following the visit, the Inspector(s) will issue the Inspection Exit Notice, in which they will note observations, which denote a deficiency or deviation from the protocol, GCP or regulations.

Each recorded observation is assigned a risk category in accordance with GUI-0043 - Classification of Observations Made in the Conduct of Inspections of Clinical Trials (Health Canada) and Procedure for reporting of GCP inspections by CHMP (INS-GCP-4) (EMA). The risk categories are: Critical (Risk 1), Major (Risk 2), Minor (Risk 3). The draft Inspection Exit Notice also includes the overall inspection compliance rating of Compliant (only minor and major observations reported) or Non-Compliant (one or more critical observations; or several major observations that are deemed to be systematic issues).

FDA's final classifications include: **No Action Indicated (NAI)** – No objectionable conditions or practices were found during an inspection or the significance of any objectionable conditions found does not justify further regulatory action., **Voluntary Action Indicated (VAI) –** Objectionable conditions or practices were found, but the Agency is not prepared to take or recommend any regulatory action since the objectionable conditions or practices do not meet the threshold for regulatory action, and **Official Action Indicated (OAI)** – Objectionable conditions and/or practices were found, and regulatory action should be recommended. The scope, severity, or pattern of the violation(s) support findings that:
1. Subjects under the care of the clinical investigator would be or have been exposed to an unreasonable and significant risk of illness or injury; or
2. Subjects' rights, welfare, or safety would be or have been seriously compromised; or
3. Data integrity or reliability is or has been compromised.

At the Closing Meeting, the Inspector may provide the QI and project team with a verbal summary of the observations made during the inspection visit, and an opportunity to ask questions. The Inspector may return to the site for a face-to-face Exit Meeting or will conduct the meeting via teleconference (usually within a few weeks of the Closing Meeting). With the receipt of the Final Exit Notice, the QI and Sponsor should prepare a formal written response to all observations with an "open" status, including corrective and preventative action (CAPA) plans, and submit by the due date.
When all responses have been reviewed by Health Canada/FDA/EMA and when no further actions in response to the observations are required, the Inspector may issue a written acknowledgement to the QI and Sponsor and the inspection cycle is closed.

For Further Assistance

In addition to the documents mentioned above, further information and guidance for researchers on the inspection process can be found in N2 SOP017_08 Audits and Inspections, available from the KGHRI. Other documents available from the KGHRI:

Audits and Inspections Checklist
EMA Guidance Documents
FDA Guidance Documents
Health Canada Inspection Package

The KGHRI is available to assist with any matters related to clinical trial inspections by Health Canada or other bodies, including trials conducted outside of the WJHCPOR but within KHSC. Please contact Lisa McAvoy, at KGH ext. 3344 or Lisa.McAvoy@kingstonhsc.ca.