



1. Purpose

The objective of this operating procedure is to delineate the steps to be followed when clinical trial audits and inspections are performed by governing regulatory bodies at either CERU or at sites participating in CERU projects.

2. Responsibilities

CERU: The responsible CERU staff members should follow the procedures as outlined in this SOP to prepare for the inspection process for a particular CERU project. Usually the responsible individual is the Project Leader.

Qualified Investigator: The Qualified Investigator at the applicable participating research sites is responsible for ensuring the study site is prepared for the inspection process.

3. Definitions

3.1 Audit: a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirements.

-ICH GCP 1.6

3.2 Inspection: The act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities 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 organization's facilities, or at other establishments deemed appropriate by the regulatory authorities.

-ICH GCP 1.29

4. Procedures

4.1 Inspections can be carried out at any time during a study. If carried out at the beginning of the study, an inspection can serve to correct errors before the study is completed; however it can be carried out at any time, in the course of the study, or at the end.

4.2 A "for cause" inspection is carried out when there is reason to believe that there are problems with the sites' data and/or procedures. It usually a specific response to a known or suspected non-compliance. Enforcement measures may be necessary.

4.3 Following notification to CERU that an inspection of a clinical trial will be conducted, at either CERU or a participating research site, by a governing regulatory agency (e.g. Therapeutic Products Directorate (Health Canada), Food and Drug Administration (USA), etc), the responsible individual(s) at CERU should do the following:



Regulatory Agency Inspections/Audits
601-01

- 4.3.1 Notify the Sponsor/Principal Investigator, CERU study team, external suppliers, site investigators, site coordinators, and the research ethics board (REB).
- 4.3.2 Create and maintain an inspection communication file. All communications and accompanying documents should be marked with the date and time of receipt or submission. All communications and accompanying documents should be filed.
- 4.4 The inspection notification will outline the purpose of the inspection and areas of intended review. In general, inspections can usually be divided into 3 main areas of review, though the scope and extent of the review is determined by the inspection agency:
 - 4.4.1 REB oversight and consent contents;
 - 4.4.2 Handling of investigational products (including manufacturers and pharmacies);
 - 4.4.3 Patient case review
- 4.5 Refer to Appendix 5.1 for a further breakdown of the areas of review.

Preparing for the Inspection

- 4.6 Following notification of the inspection, the responsible CERU staff member, and/or delegate, should immediately begin preparation activities, and if applicable coordinate with the local research site:
 - 4.6.1 Notify Kingston General Hospital and Queen's University of the inspection. Coordinate with responsible personnel from KGH and Queen's to ensure institutional procedures are followed (including any potential pre-inspection activities)
 - 4.6.2 Communicate the inspection dates and individuals who should make themselves available during the inspection;
 - 4.6.3 Determine the areas the inspector will want to visit or tour, and ensure appropriate personnel are available to accompany the inspector.
 - 4.6.4 Develop the inspection preparation plan including timelines;
 - 4.6.5 Reserve a conference room for the inspection dates (must include a telephone and convenient access to a photocopier);
 - 4.6.6 Arrange for access to patient medical records, study specific records (e.g. ICF), CRF and computer access for electronic records;
 - 4.6.7 Review the study regulatory files for completeness and accuracy;
 - 4.6.8 Review patient CRFs for completeness and accuracy (flag the relevant sections of patient medical records for ease of review);
 - 4.6.9 Ensure investigational product dispensing records are accurate, complete and available for review (if the study is blinded, external auditors reports should be made available);
 - 4.6.10 Review documentation for any instances where the study treatment was unblinded;
 - 4.6.11 Ensure investigational product accountability records are complete and accurate.
 - 4.6.12 Conduct a study team meeting prior to the arrival of the inspector to review the inspection procedures, study procedures, study protocol, CRFs, source data, and study documentation.



4.7 Refer to Appendix 5.2 for the Inspection Preparation Checklist.

During the Inspection

- 4.8 Provide the inspector with instructions on how to get to the meeting venue, and meet them at the entrance to the building.
- 4.9 Verify the identify of the inspector at the time of arrival.
- 4.10 Accompany the inspector at all times while in any study-related areas of the institution.
- 4.11 The inspector may conduct an opening meeting to meet all of the individuals involved in the study; provide an overview of the inspection process and plans for this inspection, including timelines and individuals he/she would like to meet with.
- 4.12 Ensure the entire study team is present for the opening meeting. When the inspection is conducted at a participating research site, CERU staff may be required to be present for the inspection.
- 4.13 Unless otherwise stated by the inspector, assume the Sponsor / PI should be present for the entire duration of the inspection.
- 4.14 Minutes should be taken for the duration of the inspection (from the start of the opening meeting until the exit meeting is finished). They should include reference to questions and related responses, documents reviewed and copied; individuals met with and toured facilities.
- 4.15 Orient the inspector to study records, files and computer access.
- 4.16 Provide the inspector with copies of all requested study related documents. CERU should maintain a log to record all documents copied and provided to the inspector.
- 4.17 Ensure all questions posed by the inspector are answered by the appropriate member of the study team. (Never make assumptions or guess when responding to questions. If a response is not immediately available, tell the inspector you will investigate their question and get back to them).
- 4.18 It is encouraged to always ensure there is a staff member present to assist the inspector whenever necessary. This includes arranging for coverage during lunches and breaks.
- 4.19 The inspector may conduct daily debriefing sessions at the end of the day, or at the beginning of the following day, to review any new observations, queries from the past day.
- 4.20 The inspector may conduct an exit meeting at the conclusion of the inspection. The exit meeting is an opportunity for the inspector to review all observations recorded, and for CERU, if applicable participating research site, to comment and perhaps resolve some observations before they are formalized into an inspection report.

Inspection Follow-up

- 4.21 The inspector will formalize the exit interview discussions with a formal inspection report or letter listing all of the observations and any required follow-up. This will be forwarded to the Sponsor.



- 4.22 The responsible CERU staff will circulate the inspection report to the relevant parties for follow-up and resolution.
- 4.23 Respond to the inspection report as soon as possible following receipt, but no later than any deadlines specified by the inspector.
- 4.24 Reply to each observation in the inspection report, providing clarification and the steps that were implemented to institution corrective action. Ensure that the corrective actions are completed, as promised.
- 4.25 The inspector will send correspondence to indicate the inspection process has come to a close once all observations have been addressed to their satisfaction.
- 4.26 File all inspection documentation.

5. Appendix

- 5.1 Areas of Review for Regulatory Inspections
- 5.2 Inspection Preparation Checklist

6. References

- 6.1 ICH GCP Section 1.6, 1.29: Glossary of Terms
- 6.2 ICH GCP Section 5.19: Audit
- 6.3 Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators. US Department of Health and Human Services Food and Drug Administration, January 2006.
- 6.4 Weiss RB and Tuttle SS. Preparing for Clinical Trial Data Audits. *Journal of Oncology Practice* 2006;2(4);157-59.
- 6.5 Network of Networks Standard Operating Procedures for Clinical Research ([N₂ organization](#)).

Areas of Review for Regulatory Inspections

REB Oversight and Consent Contents	Handling of Investigational Products	Patient Case Review
<p>Protocol Submission Compliance</p> <ul style="list-style-type: none"> <input type="checkbox"/> Submission of protocol and other applicable documents to REB for initial review <input type="checkbox"/> Timely annual renewals (including pertinent updates) <input type="checkbox"/> Submission of amendments <input type="checkbox"/> AE/SAE Reports <p>Consent Contents</p> <ul style="list-style-type: none"> <input type="checkbox"/> ICF contains all required sections as per ICH GCP section 4.8.10 	<p>Investigational Product Documentation</p> <ul style="list-style-type: none"> <input type="checkbox"/> Drug Accountability Records <input type="checkbox"/> Shipping and receiving invoices <input type="checkbox"/> Manufacturing and Conformance certificates (e.g. stability testing, batch records) <input type="checkbox"/> Product labels <input type="checkbox"/> Local stock proper labeling and expiration dates 	<p>Consent form</p> <ul style="list-style-type: none"> <input type="checkbox"/> Consent form signing & dating <input type="checkbox"/> Consent form filling in blanks <p>Protocol eligibility</p> <ul style="list-style-type: none"> <input type="checkbox"/> Individuals responsible for various aspects of the protocol <ul style="list-style-type: none"> ~verification of inclusion/exclusion criteria ~who obtained informed consent ~who collection AEs, SAEs <input type="checkbox"/> Degree of delegation of authority <input type="checkbox"/> Qualifications and training of responsible individuals <p>Protocol Specific Treatment</p> <ul style="list-style-type: none"> <input type="checkbox"/> Where specific aspects of the investigation are performed <input type="checkbox"/> Compliance with investigational product and procedures (clinical samples, questionnaires, etc) <p>Verification of Treatment Response & Outcome</p> <ul style="list-style-type: none"> <input type="checkbox"/> How data were recorded <input type="checkbox"/> Where data were recorded <p>Accuracy of Data Recording and Submission</p> <ul style="list-style-type: none"> <input type="checkbox"/> Patient chart/record audit

Inspection Preparation Checklist

Activity	Description	Complete	N/A	Comments
ORGANIZATIONAL ACTIVITIES				
Notify all parties	Sponsor / PI	<input type="checkbox"/>	<input type="checkbox"/>	
	REB	<input type="checkbox"/>	<input type="checkbox"/>	
	Co-Investigators	<input type="checkbox"/>	<input type="checkbox"/>	
	Site Investigators	<input type="checkbox"/>	<input type="checkbox"/>	
	Site Coordinators	<input type="checkbox"/>	<input type="checkbox"/>	
	ORS / KGH	<input type="checkbox"/>	<input type="checkbox"/>	
	Pharmacy	<input type="checkbox"/>	<input type="checkbox"/>	
	Laboratories	<input type="checkbox"/>	<input type="checkbox"/>	
	Medical Records	<input type="checkbox"/>	<input type="checkbox"/>	
	External Suppliers	<input type="checkbox"/>	<input type="checkbox"/>	
	Reserve conference room	<input type="checkbox"/>	<input type="checkbox"/>	
Arrange for computer access	<input type="checkbox"/>	<input type="checkbox"/>		
General Overview	Prepare a general overview of the study	<input type="checkbox"/>	<input type="checkbox"/>	
	List of all personnel and responsibilities delegated	<input type="checkbox"/>	<input type="checkbox"/>	
List of participants	List all participants including: name, address, phone #, date enrolled, date completed and medical record #	<input type="checkbox"/>	<input type="checkbox"/>	
	Screening Logs	<input type="checkbox"/>	<input type="checkbox"/>	
FILE MANAGEMENT				
Organize all regulatory files by general heading in chronological order	Protocol (all versions)	<input type="checkbox"/>	<input type="checkbox"/>	
	Product Monograph / Investigator's Brochure	<input type="checkbox"/>	<input type="checkbox"/>	
	Protocol Amendments	<input type="checkbox"/>	<input type="checkbox"/>	
	Clinical Trial Site Information Form	<input type="checkbox"/>	<input type="checkbox"/>	
	Qualified Investigator Undertaking Form	<input type="checkbox"/>	<input type="checkbox"/>	
	REB Attestation Form	<input type="checkbox"/>	<input type="checkbox"/>	
	CVs for QIs	<input type="checkbox"/>	<input type="checkbox"/>	
	Medical Licenses for QIs	<input type="checkbox"/>	<input type="checkbox"/>	
REB Files	Initial Approval Letter	<input type="checkbox"/>	<input type="checkbox"/>	
	Amendment Approval Letters	<input type="checkbox"/>	<input type="checkbox"/>	
	Informed Consent Forms	<input type="checkbox"/>	<input type="checkbox"/>	
	Status reports for:	<input type="checkbox"/>	<input type="checkbox"/>	
	~Annual renewals	<input type="checkbox"/>	<input type="checkbox"/>	
	~AE/SAEs	<input type="checkbox"/>	<input type="checkbox"/>	
	~Deaths	<input type="checkbox"/>	<input type="checkbox"/>	
	~Study Termination	<input type="checkbox"/>	<input type="checkbox"/>	
~Final Report	<input type="checkbox"/>	<input type="checkbox"/>		
Communications (filed chronologically)	Methods Centre Correspondence	<input type="checkbox"/>	<input type="checkbox"/>	
	REB Correspondence	<input type="checkbox"/>	<input type="checkbox"/>	
	Monitoring Log	<input type="checkbox"/>	<input type="checkbox"/>	
	Other Correspondence	<input type="checkbox"/>	<input type="checkbox"/>	

Inspection Preparation Checklist

Laboratory	Central Lab certification	<input type="checkbox"/>	<input type="checkbox"/>	
	Central Lab reference ranges	<input type="checkbox"/>	<input type="checkbox"/>	
	Local lab certification	<input type="checkbox"/>	<input type="checkbox"/>	
	Local lab reference ranges	<input type="checkbox"/>	<input type="checkbox"/>	
Investigational Product	Drug accountability logs	<input type="checkbox"/>	<input type="checkbox"/>	
	Sent and Received Invoices	<input type="checkbox"/>	<input type="checkbox"/>	
	Dispensing Logs	<input type="checkbox"/>	<input type="checkbox"/>	
	Return / Destruction Logs	<input type="checkbox"/>	<input type="checkbox"/>	
REVIEW				
Collect and review for each participant	CRF completed for each participant	<input type="checkbox"/>	<input type="checkbox"/>	
	Informed Consent Forms (completed, signed and dated)	<input type="checkbox"/>	<input type="checkbox"/>	
	Source documents for each participant that documents the following:	<input type="checkbox"/>	<input type="checkbox"/>	
	~condition at time of study entry (Incl/Excl met?)	<input type="checkbox"/>	<input type="checkbox"/>	
	~record of consent process occurring prior to initiation of any study related procedures	<input type="checkbox"/>	<input type="checkbox"/>	
	~Exposure to investigational product	<input type="checkbox"/>	<input type="checkbox"/>	
	~Concomitant medications	<input type="checkbox"/>	<input type="checkbox"/>	
	~Clinical assessments of the participant during the course of the study	<input type="checkbox"/>	<input type="checkbox"/>	
	~Laboratory reports	<input type="checkbox"/>	<input type="checkbox"/>	
	~Diagnostic tests	<input type="checkbox"/>	<input type="checkbox"/>	
	~Dose modifications	<input type="checkbox"/>	<input type="checkbox"/>	
	~AEs / Death	<input type="checkbox"/>	<input type="checkbox"/>	
	~protocol deviations/violations	<input type="checkbox"/>	<input type="checkbox"/>	
~early termination	<input type="checkbox"/>	<input type="checkbox"/>		
SITE SPECIFIC				
Temperature Logs	Refrigeration	<input type="checkbox"/>	<input type="checkbox"/>	
	Drug	<input type="checkbox"/>	<input type="checkbox"/>	
	Other	<input type="checkbox"/>	<input type="checkbox"/>	
Equipment	Calibration logs	<input type="checkbox"/>	<input type="checkbox"/>	
	Inspection reports	<input type="checkbox"/>	<input type="checkbox"/>	
	Permits	<input type="checkbox"/>	<input type="checkbox"/>	
	Licensure	<input type="checkbox"/>	<input type="checkbox"/>	