
# University of Florida Health Cancer Center

# Clinical Trial Audit Manual

**Version: 1.0**

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## ABBREVIATIONS

| | |
|---|---|
| AD-CRO | Administrative Director of the Clinical Research Office |
| ADCI | Associate Director for Clinical Investigation |
| AE | Adverse event |
| ARC | Affiliate Research Consortium |
| CAPA | Corrective and preventative action |
| CRO | Clinical Research Office |
| CTAT | Clinical Trials Auditing Team |
| CTMB | Clinical Trials Monitoring Branch |
| DISC | Data Integrity and Safety Committee |
| DOA | Delegation of authority |
| DSG | Disease Site Group |
| DSMP | Data and Safety Monitoring Plan |
| ETCTN | Experimental Therapeutics Clinical Trials Network |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICH | International Council for Harmonization |
| IIT | Investigator initiated trial |
| IRB | Institutional review board |
| NCI | National Cancer Institute |
| NCI CIRB | National Cancer Institute Central Institutional Review Board |
| NCTN | National Clinical Trials Network |
| PI | Principal investigator |
| SAE | Serious adverse event |
| UFHCC | University of Florida Health Cancer Center |

## DEFINITIONS

Active Study: Any research study that is being conducted under an active approval by an institutional review board (IRB). These studies are typically in an open to accrual or follow-up status in OnCore. Studies move into an inactive status once they have been formally closed with the IRB.

Auditing: 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, good clinical practice (GCP), and the applicable regulatory requirement(s)" International Council for Harmonization (ICH) E6 1.6.

Clinical Trial: The National Institutes of Health defines a clinical trials as "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

Critical Deficiency: As written in the Clinical Trial Monitoring Branch (CTMB) of the National Cancer Institute (NCI) Guidelines, a critical deficiency is "*any condition, practice, process or pattern that adversely affect the rights, safety or wellbeing of the patient/study participant and/or the quality and integrity of the data; includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data.*"

Intervention: The National Institutes of Health defines an intervention as "a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints." Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies."

Investigator Initiated Trial: Any clinical trial that was initiated and conducted by a sponsor-investigator. The Federal Drug Administration (FDA) defines a sponsor-investigator as "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed." **The University of Florida (UF)'s investigator initiated trials (IITs) are further characterized as trials that both originated at UF and are centrally managed by the institution**.

Lesser Deficiency: As written in the CTMB NCI Guidelines, a lesser deficiency is a finding that "does not have significant impact on the outcome or interpretation of the study and is not described above as a major deficiency." An unacceptable frequency/quantity of lesser deficiencies should be treated as a major deficiency when determining the final assessment of a component."

Major Deficiency: As written in the CTMB NCI Guidelines, a major deficiency is "a variance from protocol-specified procedures or practices that makes the resulting data questionable."

Principal Investigator: An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the study intervention is carried out on a participant). In the event an investigation is conducted by a team of individuals, the principal investigator (PI) has the ultimate responsibility for the conduct of the research project.

Sub-Investigator: Any other member of the research team who will make clinical decisions during the research or make a direct and significant contribution to the data. The ICH Good Clinical Practices (GCP) Guideline defines a sub-investigator as "any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions."

## I. INTRODUCTION/BACKGROUND

Auditing is a function that is distinct from routine monitoring and quality control processes. The primary purpose of an audit is to evaluate overall study conduct and compliance with the protocol, the sponsor's standard operating procedures, the GCP Guidelines, and regulatory requirements at a very high level. This is not interchangeable with monitoring, which is a continuous function, though there is overlap with the study content that is reviewed.

The Clinical Trials Auditing Team (CTAT), which comprises of staff from the UF Health Cancer Center (UFHCC) Clinical Research Office (CRO), is responsible for conducting internal audits of applicable clinical trials. Trials are selected for audit per the guidelines outlined by this audit manual and the UFHCC Data and Safety Monitoring Plan (DSMP). The CTAT conducts quality assurance audits of all clinical trials conducted by the UFHCC, UF IITs, and National Clinical Trials Network (NCTN) studies conducted by UFHCC Affiliate Research Consortium (ARC) sites. The CTAT follows guidelines based upon those established by the CTMB of the NCI. During audits, a CTAT member, or members, will compare submitted data with corresponding source documentation and assess protocol and regulatory compliance, informed consent accuracy and documentation, eligibility, treatment administration, response evaluation, adverse events (AEs), overall data quality, IRB documentation, and pharmacy records.

## II. SCOPE

This manual applies to all active clinical trials conducted at UFHCC, regardless of sponsorship. This manual also applies to UF IITs and NCTN studies conducted at ARC sites. The NCI defines a clinical trial as "a prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies." Trial participants may include current or former cancer patients, persons without cancer who may be at risk for developing cancer, or healthy volunteer controls enrolled in cancer-relevant studies.

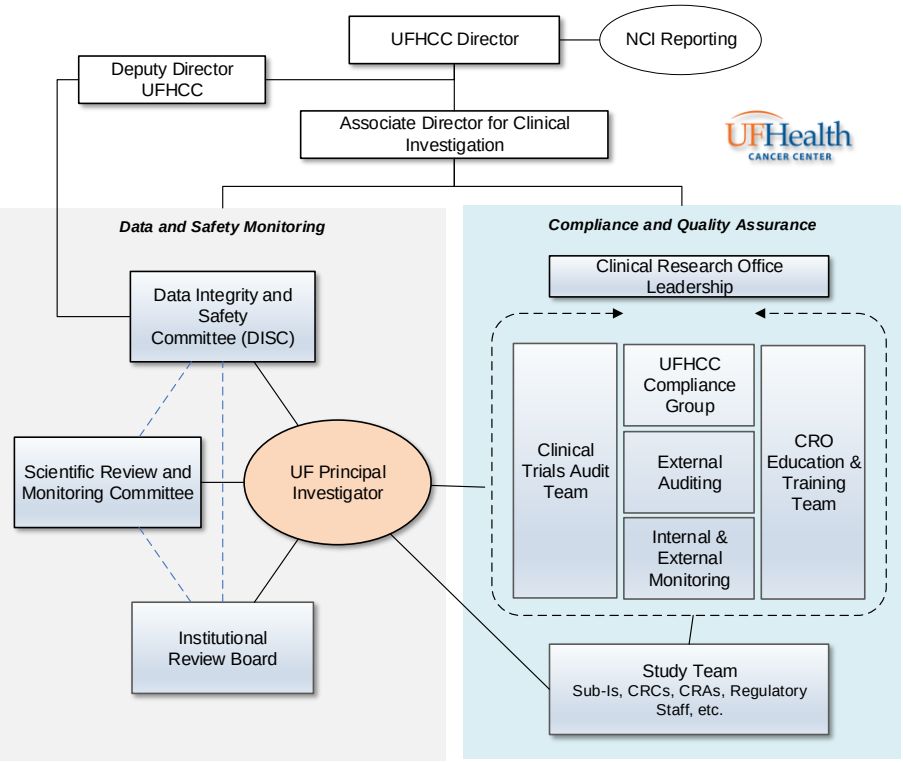
UF defines a cancer-relevant study as one that meets at least one of the following criteria:

- Specifies enrolling patients with a known or suspected diagnosis of cancer as part of the eligibility criteria;
- Includes research endpoints related to cancer, associated symptoms, or established cancer risk factors (including smoking and tobacco-associated studies, surveys, hepatitis or human papilloma virus vaccines, etc.); or
- The local PI plans to exclusively enroll current, former, or potential cancer patients into the study

## III. CLINICAL TRIALS AUDITING TEAM

The CTAT provides ongoing auditing for complex through low-risk clinical trials. Audits are conducted per the outlined review frequency in the UFHCC DSMP. Routine, random, and "for cause" audits may be conducted for any cancer-relevant externally sponsored studies. All auditing activities are performed in accordance with the ICH GCP Guidelines. The CTAT audit process is also intended to evaluate the

effectiveness of current training, education, and monitoring practices. Findings may translate to modifications in standard operating procedures, policies, or research oversight system activities.




The CTAT has full authority to access research and pertinent clinical records of all patients enrolled in studies that fall under its review. This is done in the interest of current and future subjects as well as non-study patients that may be impacted by the results of our trials.

Formal reports summarizing the findings of audits with identification of any specific findings warranting creation of a corrective and preventative action (CAPA) plan are provided to the PI and study team for review and response. CTAT audit reports are also provided to the Associate Director for Clinical Investigation (ADCI) and the Administrative Director of the CRO (AD-CRO).

## IV. UFHCC COMPLIANCE GROUP

The UFHCC Compliance Group was formed to systematically evaluate the UFHCC internal audit findings and to identify any potential clinical or operational barriers to research compliance.

### *Meeting Structure & Responsibilities*

The Compliance Group meets monthly to ensure timely oversight of internal and external audits. The group reviews all internal audit reports provided by the CTAT and discusses the protocol audit findings. The group makes recommendations regarding when additional corrective action(s) and/or additional education is needed to ensure improvements in quality and research compliance.

The group provides a monthly summary to the Data Integrity and Safety Committee (DISC) of the audits reviewed and any issues that were identified at the last meeting. In addition, the Compliance Group can refer any major problems that have been identified to the DISC for consideration and possible immediate action.

At each convened DISC meeting, the DISC reviews the audit summaries and findings and determines if additional corrective action is necessary.

### *Membership*

Membership includes representation from UFHCC leadership and CRO staff including:

- The ADCI
- The AD-CRO
- Division of Quantitative Sciences
- Project Management and Regulatory Affairs
- Clinical Research Administration and Compliance
- Study Coordination and Data Management

A group roster is stored within the UFHCC Administrative Office.

## V. GENERAL AUDIT OPERATIONS

The audit process begins with the selection of a protocol. The CTAT selects protocols according to set criteria, such as DISC assignment, risk level as assigned by the Scientific Review and Monitoring Committee (if applicable), disease site group (DSG), time since last audit, requests for audit, new investigators and/or study coordinators, and number of subjects accrued. Once the protocols have been chosen, the trial is assigned to a CTAT auditor. Assignments are based on the auditor's current caseload and individual knowledge base of the assigned protocol and/or disease site.

The CTAT auditor contacts the PI and study team via email with information to review in preparation for the audit approximately 2 weeks in advance of the audit. The email contains the audit notification, which describes the audit proceedings, how to prepare for the audit, and a list of randomly selected subjects to be audited. During the audit, the CTAT auditor compares the medical records and research files to the protocol and submitted forms to verify compliance with protocol and regulatory requirements as well as the accuracy of data collection.

It is important for the PI and study team to be available during the audit to assist the CTAT auditor as needed. The CTAT auditor completes an audit review form for each subject reviewed to assess data collection and protocol compliance as documented in the record. Following the audit, the CTAT auditor will conduct an exit interview with the PI and study team. During the exit interview, the PI and study team will have an opportunity to verbally discuss the preliminary findings, recommendations, or questions that have arisen during the audit. In situations where missing data has been identified, the PI and study team will be given 2 business days to produce the requested documentation.

The PI and study team will be sent a final letter of audit findings via email within 5 business days following the exit interview. The PI will be asked to acknowledge receipt of the audit report and reply with a CAPA plan, if applicable, via email. The Compliance Group will then assess the PI's response to determine if further action is necessary. The group communicates this information to the DISC Administrator approximately 2 weeks prior to the DISC review meeting. DISC is responsible for communicating any additional recommendations or requirements to the PI and study team following committee review of the findings.

An affiliate (ARC member) site may be audited separately or in conjunction with the main institution. If an affiliate site is to be audited separate from the main institution, they will be notified separately of the main institution and a separate audit report will be generated for each affiliate site that is audited.

Timelines listed here are ideal; however, there may be some variations in practice due to limitations in scheduling/availability.

## VI. PROTOCOL SELECTION

The lead CTAT auditor is responsible for selecting and scheduling audits for the CTAT. Audits of clinical trials subject to the UFHCC's research oversight system will be scheduled according to the guidelines outlined in the UFHCC DSMP.

| Protocol Prioritization | Audit Frequency |
|---|---|
| UF IIT or DISC monitoring required | Follows the monitoring frequency chart found in the DISC Charter. |
| UF IITs conducted at ARC sites | At a minimum, the first subject enrolled on a UF IIT protocol at a UFHCC ARC member site will be audited. This is in addition to the level of monitoring required per assigned monitoring plan for that specific protocol. |
| NCTN/Experimental Therapeutics Clinical Trials Network (ETCTN) trials | At a minimum, each NCTN/ETCTN study will be audited annually. At least 10% or a minimum of 2 cases will be selected from each study. |
| Externally sponsored studies | At a minimum, 2 externally sponsored studies from each DSG (not including NCTN or ETCTN trials) will be audited annually. At least one case will be selected from each study. |
| New PIs | At a minimum, one enrolled subject and up to 3 additional subjects will be audited within the PI's first year. These cases are separate from required DISC, NCTN/ETCTN, and/or DSG based auditing requirements. |
| New coordinators | At a minimum, one enrolled subject and up to 3 additional subjects will be audited within the coordinator's first year. These cases are separate from required DISC-, NCTN/ETCTN-, and/or DSG-based auditing requirements. |
| For cause | As needed. |

## VII. SUBJECT SELECTION

Subject selection for routine audits will be completed using a randomizing program and will represent a minimum number of enrolled study subjects for the selected protocol as outlined in the UFHCC DSMP. The number of subjects selected may vary depending on the protocol prioritization chart in Section VI. PROTOCOL SELECTION). Subject selection is random, impartial, and will take into account subjects accrued during the specified audit review period. In order to maintain the highest quality protocol-specific research data, subject charts will be audited thoroughly for informed consent documentation, original source documentation required to support protocol compliance, and other relevant information. Usually, only cases entered since the last audit will be selected, but any accrued

cases (even those that were previously audited) might be selected. In situations where a previously audited case is selected, only activities occurring after the prior audit will be reviewed.

## VIII. AUDIT SCHEDULING

A scheduled audit date will be set for a time that is mutually convenient for both the auditors and the site. The type of audit will be specified as either full, process, mock, routine, or "for cause." The assigned CTAT auditor will notify the study PI and primary study coordinator of pending routine audits approximately 2 weeks in advance. Advance notification for a "for cause" audit is not required. The lead and affiliate sites for multi-institution trials may be notified together or separately. The auditor will communicate the audit process via email and will include the following:

- A full inventory of items to be audited including all announced subject cases
- Logistics, including the date, time, and location of the audit
- A request for exit interview scheduling
- A link to this UFHCC Audit Manual and the UFHCC DSMP for review of the research oversight system and audit process, as applicable

The PI and/or primary study coordinator should make every effort to be available for questions on the date(s) selected.

## IX. PREPARING FOR AN AUDIT

Prior to the audit, the PI and study team are responsible for gathering and organizing all records in preparation for the audit. It is expected that the auditor will have access to all required documents and the information be organized in such a way as to be easily located and identified. The PI and study team must plan to have records available to the CTAT auditor(s) at the designated audit location. If the CTAT auditor is expected to audit electronic documents, it is the responsibility of the PI and study team to ensure that the CTAT auditor is granted access throughout the audit process.

### *The Clinical Trials Auditing Team Auditor*

Prior to the audit, the CTAT auditor is responsible for the following:

1. Review of accrual information in OnCore, which includes new subjects enrolled since the last visit, previously audited subjects, and completed (fully reviewed) subjects.
2. Review of the protocol regulatory files to verify/request availability of:
    a. IRB initial approval
    b. IRB approval of amendments
    c. IRB approval of annual continuing reviews
    d. A current and approved version of the protocol and informed consent document
    e. Reported AEs
    f. IRB written approval of the protocol from any affiliate institution involved in the audit
3. Review of prior audit records and findings
4. Two business days before the audit, the CTAT Auditor will email or call a member of the study team to confirm the date and place of the final audit and to indicate whether any documentation is missing. This will give the study team an opportunity to find this documentation for the audit visit.

### *The Principal Investigator and Study Team*

Prior to the audit, the PI and study team are responsible for the following:

1. Gathering all inpatient and ambulatory records for the selected subjects related to the conduct of the trial
2. Gathering completed case report forms and research files for the selected subjects
3. Obtaining access to required electronic data capture systems that the CTAT auditor will need to use when verifying source documentation in advance of the CTAT auditor's arrival (e.g., REDCap or other data reporting tools)
4. Contacting the pharmacy to arrange access to Vestigo to review all records regarding the dispensing of investigational product, if applicable
5. Compiling original eligibility checklists, consents, and off-study forms for the selected subjects
6. Ensuring all source documentation is available to the auditor
7. Creating documentation to address discrepancies that require clarification for the research record
8. Ensuring the regulatory binder is complete and up-to-date
9. Uploading the following study-related and subject-related documentation in OnCore (as applicable):
    a. All IRB records, such as all protocol and consent versions and their approval letters as well as records of all revisions
    b. All subject records that are related to the study, such as all signed consents, all study-related visits, procedures, results, AEs, serious AEs (SAEs), and deviations
10. Communicating with other participating sites as the lead sit, which will have subjects selected
11. Ensuring all requested cases are delivered to the designated audit area or the audit

**PLEASE REFER TO XVIII. APPENDICES**

Appendix A. Study Documentation Audit Checklist, Appendix B. Subject Audit Checklist, and Section X. AUDIT TYPES AND ASSOCIATED PROCEDURES) for items that will be audited.

### *During the Audit Visit*

At visit initiation, the CTAT auditor is responsible for signing in on the UFHCC Audit and Monitoring Log. The original document is to be filed under the appropriate tab of the regulatory binder. If the trial is industry sponsored, the original document will be kept in the appropriate binder located in the UFHCC CRO. The PI and study team are responsible for providing access to the required medical records, research files, and other documentation. CTAT auditors are encouraged to contact the PI or study team members during the audit to attempt to resolve any questions that may arise. This will help to avoid erroneous violations from being cited and result in a more accurate assessment of protocol and regulatory compliance and data verification. The CTAT auditor will complete an audit review form for regulatory, pharmacy (if applicable), and each subject selected. At the exit interview, the CTAT auditor is responsible for obtaining the signature of a study team member on the UFHCC Audit and Monitoring Log.

## X. AUDIT TYPES AND ASSOCIATED PROCEDURES

### *Full Audits*

A full audit is a complete and comprehensive review of all protocol-specific activities. A full audit will usually include a review of the following, but can vary slightly:

1. Regulatory (may include, but not limited to)
    a. Documentation of initial IRB approval
    b. Documentation of annual renewal
    c. Documentation of IRB submission and approval for all amendments and revisions
    d. Documentation of SAE/UP submission and acknowledgement/approval, if applicable
    e. Submission and acknowledgement/approval of safety reports, if applicable
    f. IRB submission or filing (as appropriate) of other study submissions including deviations and other correspondence
    g. Informed consent content
    h. Completed delegation of authority (DOA) logs
    i. Completed training logs
    j. Investigational new drug or exemption documentation, as applicable
    k. IRB Membership list
    l. Essential Documents
2. Subject Case (may include, but not limited to)
    a. Informed Consent
    b. Eligibility
    c. Registration
    d. Treatment
    e. Drug Accountability (if applicable)
    f. Disease Outcome/Response
    g. Follow-Up
    h. AEs and SAEs
    i. Concomitant medications
    j. Toxicities
    k. Lab Tests/Study Procedures
    l. Data Quality
    m. Protocol deviations and/or violations
    n. Other (at the CTAT auditor's discretion)
3. Pharmacy (may include, but not limited to)
    a. Drug inventory records, including orders, transfers, and returns
    b. Temperature control logs
    c. Investigational agent expiration dates
    d. Pharmacy Manual, if applicable per study
    e. Training logs

Formal reports summarizing the findings of audits with identification of any specific findings warranting a CAPA plan are provided to the PI for review and response. A copy of the formal audit report will also be provided to the DISC Administrator, ADCI, and AD-CRO.

### *Process Audits*

A process audit is a systematic review of the clinical trial process and is typically a less detailed review than a full audit. Process audits are done on an as needed basis. Process audits are intended to identify areas for improvement by evaluating trends in conduct and compliance. Process audits are also useful in identifying successful processes and providing positive feedback to study teams. Upon completion of a process audit, results are reported to identify positive trends that should be reinforced and negative trends to be addressed through training, policy revisions, and/or corrective and preventative action planning. The scope of a process audit will vary and may focus on trials of a certain type, trials under a specific investigator or study team, or for cause as needed.

- "A process audit is assigned by using information from various sources. These sources may include trends observed during the conduct of other internal/external audits and inspections, concerns raised by various oversight committees, and/ or input from other clinical research team members."
- A report summarizing the findings of the audit will be provided to the PI and DISC (when the study is under DISC oversight). If any significant non-compliance is identified during a process audit, a full audit will be scheduled and the procedures for a full audit will begin.

### *Mock Audits*

Mock audits are informal audits performed to assist in preparation for a scheduled or anticipated inspection by the FDA, the National Institutes of Health, NCI, NTCN groups, ETCTN, study sponsors, or other regulatory authorities. The primary purpose of a mock audit is to assist the PI in identifying any issues of non-compliance not previously noted. Mock audits can also be requested through the UFHCC CRO website.

- The CTAT may review any or all of the items typically included in a full scope audit. An assigned CTAT auditor will coordinate with the PI to determine priority areas for review. The extent of the review will depend on the type of trial, the areas of greatest perceived risk, and time/resource constraints.
- Informal reports summarizing the findings of audits will be provided to the PI and study team. If any significant non-compliance is identified during a mock audit, a formal report summarizing the findings of the audit with identification of the specific findings warranting a CAPA plan will be provided to the PI and study team for review and response, DISC Administrator, ADCI, and AD-CRO.

### *Re-Audits*

The CTAT auditor should verify which components are to be re-audited. All components deemed as satisfactory or needs follow up could be re-audited. All components found to be unacceptable will undergo a re-audit. It is advised that the auditors review the audit report from the previous audit that necessitated the re-audit and any prior CAPA plan. The focus of the re-audit should be to assess whether the CAPA plan from the previous audit has been completely and effectively implemented.

## XI. AUDIT FINDINGS

Once the internal audit is complete, the CTAT auditor will conduct an exit interview with the PI and study team to discuss preliminary findings. The CTAT team member will generate a complete report of

their findings. All reports will be viewed and approved by the Assistant Director of Clinical Research Administration and Compliance. Final reports will be distributed to the PI and DISC Administrator (if applicable) within 5 business days of the exit interview.

| **Audit Evaluation** | **Criteria** |
|---|---|
| Exceptional | Complete source documentation, outstanding data quality, protocol compliance and regulatory compliance demonstrated. No major violations.<br>• No major violations<br>• ≤1 lesser violations per audited case<br>• PI acknowledgement required |
| Satisfactory | • No major violations<br>• ≤3 lesser violations per audited case<br>• PI acknowledgement required |
| Satisfactory, needs follow up | • One or more major violations (ratio of major to audited cases <0.5)<br>• Four to 6 lesser violations per audited case<br>• PI response and CAPA plan required |
| Unacceptable | • Critical or major violations (ratio of major to audited cases ≥0.5)<br>• A single life-threating major violation on a subject case<br>• A single major violation that questions the PI's available to conduct research per established regulations and policies<br>• Excessive lesser violations (>6 per audited case)<br>• Misconduct or fraud<br>• PI response and CAPA plan required. |

All protocols deemed "unacceptable" or requiring immediate action will be followed up with a complete audit report review and protocol status update at the next scheduled Compliance Group meeting.

## XII. CRITICAL, MAJOR, AND LESSER DEFICIENCIES

Critical, major, and lesser deficiencies are determined per NCI guidelines established by the CTMB of the NCI when grading audit findings. See Appendix C. Audit Deficiencies Reference Chart for a list of examples of potential major and lesser deficiencies.

The following are general guidelines for interpreting major and lesser deficiencies:

- Major deficiencies are considered serious. They require corrective action by the PI and study team.
- Lesser deficiencies are expected to occur occasionally. The Compliance Group will evaluate the number of lesser deficiencies to observe for any patterns.

If a subject safety risk is discovered during an audit, the CTAT auditor must notify the ADCI and the Compliance Group immediately. The members must review the violations (in person or remotely) and determine if the audit results should be submitted to the DISC for expedited review. The DISC has an opportunity at this point to recommend immediate action to the PI, such as closure of accrual and/or conduct or suspension of the protocol, if it is deemed necessary. Any DISC recommendation to suspend

or terminate a study will be communicated directly to the PI, with copies to the Scientific Review and Monitoring Committee, ADCI, UFHCC Director, and the UF IRB. Immediate action by the DISC would take place in the event of suspected subject safety risks, research fraud, or an extremely deficient audit.

## XIII. EXIT INTERVIEW

The exit interview is an opportunity to connect with the PI and study team to provide positive feedback and to address any questions that may have come up during the audit. The exit interview is also an ideal time to address any identified issues of non-compliance and to discuss any identified areas for process improvement.

During the exit interview, the CTAT auditor(s) will review a list of preliminary observations with the PI and study team. A final report will not be available at the exit interview. The grading of findings as critical, major, or lesser will be included in the final audit report and will include information shared during the exit interview and follow up period.

If documentation was not located by or available to the auditor during the scheduled audit visit, the study team will be given a short window (2 business days) following the exit interview to get this documentation to the auditor. These 2 days will apply towards the 5-day window for final report distribution to PI. The study team may resolve all discrepancies or concerns during the exit interview. Issues that are resolved during the exit interview will not be included in the final report. However, any corrections made after the exit interview will still be included in the final audit report and listed as resolved on the final report. It is recommended and encouraged that study team members participate in discrepancy resolution during the exit interview whenever possible.

## XIV. AUDIT RESPONSE REVIEW AND SUBMISSION

A report detailing the initial audit findings, who was present during the exit interview, clarifications by the staff, and any recommendations by the CTAT auditor will be submitted to the PI and primary study coordinator within 5 business days following the exit interview (Appendix D. Summary of Audit Findings (Example)). The PI will have 5 business days to acknowledge the report and address the findings, if required, for audits that are evaluated as “Satisfactory, needs follow up.” For the reports that include critical or major deficiencies, the PI must respond with a CAPA plan within 5 business days. After the receipt of the PI’s response and CAPA plan, if applicable, a final copy of the detailed report of audit findings and PI’s response will be presented to DISC for review. If the PI fails to provide a response within the allotted time frame or the response is inadequate, then t DISC may recommend study suspension to the Scientific Review and Monitoring Committee until an acceptable response is received, or terminated, per the discretion of the DISC Chair or Vice Chair.

## XV. CORRECTIVE AND PREVENTITIVE ACTION PLAN

Audits resulting in a “Satisfactory, needs follow-up” may require a CAPA plan (Appendix E. Corrective and Preventative Action Plan Template) to address the observed deficiencies. If a CAPA plan is required, this will be communicated in the audit letter provided to the study team. All audits that result in “Unacceptable” will require a CAPA plan to address any observed deficiencies. The timing of CAPA plan submission is outlined above.

## XVI. MAINTENANCE OF AUDIT INFORMATION

### *Audit repository*

Data from the completed audit reports is entered into OnCore under the Auditing/Monitoring tab and completed audit reports are uploaded into OnCore.

### *Audit logs*

Logs of completed audits are uploaded into OnCore.

## XVII. REFERENCES

1. US Department of Health and Human Services, the Food and Drug Administration, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). March 2018. URL: https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf.

2. University of Florida Health Cancer Center. Data and Safety Monitoring plan. September 2018. URL: https://cancer.ufl.edu/clinical-trials-2/clinical-trials-office-2/research-oversight-system/data-integrity-and-safety-committee/.

3. National Cancer Institute. Addendum to CTMB Audit Guidelines. March 2014. URL: https://ctep.cancer.gov/content/docs/Addendum_to_CTMB_Audit_Guidelines.pdf.

4. National Cancer Institute. NCI Guidelines for Auditing Clinical Trials for the NCI National Clinical Trials Network (NCTN) Program including NCI Community Oncology Research Program (NCORP) and NCORP Research Bases. September 6, 2017. URL: https://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf.

## XVIII. APPENDICES

### *Appendix A. Study Documentation Audit Checklist*

| **Study Documentation Audit Report** | |
|---|---|
| **Protocol ID:** | **PI:** |
| **Audit Date:** | **Auditor:** |

| | ITEM | YES | NO | N/A | Comments |
|---|---|---|---|---|---|
| **IRB History** | 1. Was initial approval by an expedited review instead of a full-board review? | | | | |
| | 2. Did any registration/treatment take place prior to full IRB approval? | | | | |
| | 3. Is the most recent version of the protocol on file? | | | | |
| | 4. Are there previous versions of the protocol? | | | | |
| | 5. If yes, are they on file? | | | | |
| | 6. Is the initial IRB approval letter on file? | | | | |
| | 7. Did the study have IRB approval throughout? | | | | |
| | 8. Was there an expired/delayed re-approval? | | | | |
| | 9. Did the IRB approve all versions of the protocol, informed consent and investigator's brochures? | | | | |
| | 10. Are all IRB-approved study advertisements or patient materials present? | | | | |
| | 11. Is all correspondence with IRB on file? | | | | |
| | 12. Have there been any changes to the study? | | | | |
| | 13. If yes, were any amendments approved by IRB before implementation? | | | | |
| | 14. Is there screening and enrollment log? | | | | |
| | 15. Is there an eligibility checklist containing inclusion/exclusion criteria? | | | | |
| **Study Staff** | 16. Is the delegation of authority log with signatures complete/updated and accurate? | | | | |
| | 17. Do all individuals performing study activities, have tasks assigned in the DOA? | | | | |
| | 18. Did the study staff have IRB approval? | | | | |
| | 19. Is there documentation of complete/updated study-specific training for all study staff? | | | | |
| | 20. Are there CVs of the PI/Investigators on file? | | | | |
| | 21. Are they updated within the past 2 years? | | | | |
| | 22. Are CVs signed and dated? | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Regulatory Essentials** | 23. Are there copies of all signed versions of the FDA 1572 (drugs or biologics studies) or Investigator Agreement (device studies)? | | | | |
| | 24. Were all the appropriate investigators listed on the 1572/Investigator Agreement? | | | | |
| | 25. Are there Financial Disclosures for all investigators listed on the 1572/ Investigator Agreement? | | | | |
| | 26. Are there CVs and licenses covering dates of the research for all investigators listed on the 1572/ Investigator Agreement? | | | | |
| | 27. Are all versions of IB or device manual on file? | | | | |
| | 28. Is there a package insert or product information on file? | | | | |
| **Protocol Deviations** | 29. Were there changes to the research without IRB approval? | | | | |
| | 30. Were protocol deviations reported appropriately to the sponsor in regards to type and time of report? | | | | |
| | 31. Were protocol deviations reported appropriately to the IRB in regards to type and time of report? | | | | |
| | 32. Were protocol deviations reported appropriately to the DISC in regards to type and time of report? | | | | |
| **Unanticipated Problems, Adverse Events** | 33. Have all UPs/AEs/SAEs been reported to IRB as required? | | | | |
| | 34. Have all AEs/SAEs been reported to sponsor as required? | | | | |
| | 35. Have all AEs/SAEs been reported to DISC as required? | | | | |
| | 36. Was there documentation of review, grade, and attribution of AEs by the PI or other qualified staff member? | | | | |
| **IP Accountability** | 37. Is drug accountability on file? | | | | |
| | 38. Does balance of IP on file match physical inventory? | | | | |
| | 39. Was the IP/device used to treat according to the protocol and not for other purposes? | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | 40. Were there separate records for multiple agents? | | | | |
| | 41. Are there instructions for handling/storage of the IP on file? | | | | |
| | 42. Is the IP stored in accordance with the instructions? | | | | |
| | 43. Is there a record for investigational product dispensation? | | | | |
| | 44. Is there documentation of drug dispensing for each subject? | | | | |
| | 45. Are there shipping/receiving receipts on file? | | | | |
| | 46. Is the temperature monitoring log up to date? | | | | |
| | 47. Is there appropriate documentation for the return or destruction of study drug? | | | | |
| | 48. Was the IP destroyed/returned in accordance with protocol? | | | | |
| | 49. Are procedures in place and followed to ensure that the person prescribing and cosigning prescriptions for IP is an authorized prescriber for the protocol and an order for IP is signed or cosigned by an authorized investigator prior to IP dispensing and administration? | | | | |
| | 50. If a drug study, was the drug kept in the IDS? | | | | |
| | 51. If a device study, was the device kept in a secure place and labeled “investigational”? | | | | |
| | 52. Was the device maintained and disposed in accordance with the IRB-approved plan for device maintenance? | | | | |
| **Lab** | 53. Are laboratory tests required? | | | | |
| | 54. Is there a copy of current normal laboratory values on file? | | | | |
| | 55. Is there documentation of validation or calibration? | | | | |
| | 56. Is there a current laboratory certification on file? | | | | |
| | 57. Is there a signature log for all laboratory staff? | | | | |

| | ITEM | YES | NO | N/A | Comments |
|---|---|---|---|---|---|
| **General considerations** | 58. Were the documents neatly organized? | | | | |
| | 59. Was the data kept in an appropriate and secure place? | | | | |
| | 60. Were there blank case report forms included as part of the essential documentation? | | | | |

| | ITEM | YES | NO | N/A | Comments |
|---|---|---|---|---|---|
| **Multisite Studies When UFHCC is the Coordinating Site** | 61. Are the 1572s or Investigator Agreements from all sites present? | | | | |
| | 62. Are the CVs from all sites present? | | | | |
| | 63. Is there documentation that the sponsor-investigator supplied the IB/device manual to all sites? | | | | |
| | 64. Is there documentation that the sponsor-investigator has obtained financial disclosure information and/or changes to financial information from all sites? | | | | |
| | 65. Is there documentation that the IP was shipped to the investigators conducting the study? | | | | |
| | 66. Is there documentation that the sponsor-investigator has maintained adequate records showing the receipt, shipment, or other dispensation of the IP at all sites? | | | | |
| | 67. Is there documentation of the return of all unused IP at all sites? | | | | |

**Comments:**

## *Appendix B. Subject Audit Checklist*

| **Subject Audit Report** | |
|---|---|
| **Protocol ID:** | **PI:** |
| **Subject Study ID:** | **Subject #:** |
| **Date of Consent:** | **Consent Version Date:** |
| **Audit Date:** | **Auditor:** |

| | ITEM | YES | NO | N/A | Comments |
|---|---|---|---|---|---|
| **Consent** | 1. Was the correct version of the informed consent used? | | | | |
| | 2. Was the ICF signed and dated by the subject? | | | | |
| | 3. Was the ICF signed and dated by the PI or an authorized designee? | | | | |
| | 4. Was the re-consent required? | | | | |
| | 5. Was the re-consent signed and dated by the subject? | | | | |
| | 6. Was the re-consent signed and dated by the PI or an authorized designee? | | | | |
| | 7. Was the translated consent or short form provided to the study participant and/or LAR? | | | | |
| | 8. Did the consenting individual, subject or LAR sign and date their own entry? | | | | |
| | 9. Was the consent executed and ICF signed prior to study procedures? | | | | |
| | 10. Was the consent process documented and the documentation is available? | | | | |
| | 11. Was a signed copy of ICF given to the subject/LAR? | | | | |
| **Eligibility** | 12. Did the study participant meet all eligibility criteria per protocol? | | | | |
| | 13. Has the reason for eligibility failure been documented in the source documents? | | | | |
| | 14. Do the source documents verify that all eligibility criteria have been met? | | | | |
| | 15. Have the study coordinator and the PI or Sub-I signed and dated the eligibility verification? | | | | |
| | 16. Have all pre-enrollment procedures been completed per protocol? | | | | |
| | 17. Is the subject's medical history documented per protocol? | | | | |
| | 18. Have all current and prior medications been documented per protocol and | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | linked to the appropriate medical diagnosis? | | | | |
| **Randomization** | 19. Were stratification criteria correct? | | | | |
| | 20. Was the subject registered/randomized correctly? | | | | |
| **Treatment** | 21. Did the study participant receive the correct study intervention and in correct sequence? | | | | |
| | 22. Was additional agent/treatment/intervention used which was not permitted by the protocol? | | | | |
| | 23. Were all dosages calculated and administered correctly? | | | | |
| | 24. Were dose modifications justified? | | | | |
| | 25. Were dosage modification done as outlined by the protocol? | | | | |
| | 26. Was the study participant compliant with the dosing/treatment schedule? | | | | |
| | 27. Were treatment dates correct? | | | | |
| | 28. Were any delays in therapy justified? | | | | |
| | 29. Were RT doses correct? | | | | |
| | 30. Were the delays in RT justified? | | | | |
| | 31. Were all required visits, tests and procedures performed in accordance with the protocol? | | | | |
| **Response** | 32. Are recorded initial sites of disease involvement documented? | | | | |
| | 33. Are initial tumor (disease criteria) measurements documented? | | | | |
| | 34. Were the tumor (disease criteria) measurements performed as per protocol? | | | | |
| | 35. Was the frequency of measurements performed as per protocol? | | | | |
| | 36. Were protocol response criteria followed? | | | | |
| **AEs** | 37. Has the study participant experience any AEs or SAEs? | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | 38. Were all AEs reported on the case report form in compliance with the protocol? | | | | |
| | 39. Were all SAEs reported to the study sponsor and IRB in compliance with the protocol, IRB requirements? | | | | |
| | 40. Were all SAEs reported to the DISC? | | | | |
| | 41. Is there documentation of any follow-up of SAEs? | | | | |
| | 42. Did the SAE result in the subject's removal from the study? | | | | |
| | 43. Have all AEs and/or SAEs been followed to resolution? | | | | |
| | 44. Has the PI or Sub-I as delegated by the PI documented a prompt review, grade and attribution of all AEs and/or SAEs? | | | | |
| **Follow-up** | 45. Was the frequency of observation as per protocol? | | | | |
| | 46. If the subject is off study, can survival data be obtained? | | | | |
| | 47. Is follow-up current? | | | | |
| | 48. If follow-up is not current, is the subject lost to follow-up? | | | | |

| | **ITEM** | **YES** | **NO** | **N/A** | **Comments** |
|---|---|---|---|---|---|
| **General Considerations** | 49. Does the source documentation show PI/Sub-I involvement and oversight? | | | | |
| | 50. Is the documentation submitted timely? | | | | |
| | 51. Is the documentation adequate to support compliance with the protocol? | | | | |
| | 52. Does all source documentation match the case report form entries for this subject? | | | | |
| | 53. Are there any outstanding queries for this subject? | | | | |
| | 54. Have all source document corrections been handled per GCP guidelines? | | | | |

**Comments:**

## *Appendix C. Audit Deficiencies Reference Chart*

| **IRB History Review** | |
|---|---|
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Initial approval by expedited review instead of full-board review<br>• Expedited re-approval for situations other than approved exceptions<br>• Registration and/or treatment of patient prior to full IRB approval<br>• Re-approval delayed greater than 30 days, but less than one year<br>• Registration of patient on protocol during a period of delayed re-approval or during a temporary suspension<br>• Missing re-approval<br>• Expired re-approval<br>• Some study staff is not approved by IRB<br>• Internal reportable adverse events reported late or not reported to the IRB<br>• Unanticipated problems, Serious Non-Compliance and/or Continuing Non-Compliance (per OHRP) problems not reported<br>• Lack of documentation of IRB approval of a protocol amendment that affects more than minimal risk or IRB approval is greater than 90 days following protocol release<br>• Failure to submit or submitted after 90 days, any reportable external safety report to the IRB that is considered an unanticipated problem as defined by OHRP, unless there is a local IRB policy that does not mandate reporting of external safety reports<br>• Several missing documents<br>• Other (explain) |
| **Lesser Deficiencies** | • Protocol re-approval delayed 30 days or less<br>• Delayed re-approval for protocol closed to accrual for which all study participants have completed therapy<br>• Amendment/Investigator Brochure editorial or administrative in nature or other relevant document not submitted in a timely fashion to the IRB<br>• Few missing documents<br>• Other (explain) |
| **Regulatory Documentation Review** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • No 1572 (when applicable) or Investigator Agreement (when applicable)<br>• 1572 (when applicable) signatures are missing<br>• No approved investigational new drug or exempt letter<br>• No Financial Disclosures or some are missing<br>• Several missing documents<br>• Other (explain) |
| **Lesser Deficiencies** | • IB or device manual are not on file<br>• No package insert or product information on file<br>• Not all appropriate investigators are listed on the 1572<br>• CVs of investigators are not updated, signed or dated (within the last 2 years)<br>• Other (explain) |

| **Informed Consent Content Review** | |
|---|---|
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate;<br>a. Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures<br>b. Description of foreseeable risks or discomforts<br>c. Description of any benefits to subjects or others<br>d. Disclosure of alternative procedures or treatments<br>e. Description of the extent of confidentiality of records<br>f. Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs<br>g. Explanation of whom to contact for answers to pertinent questions about the research and whom to contact for questions related to research subject's rights<br>h. Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time<br>i. Unforeseeable risks to subject, embryo or fetus<br>j. Statement that circumstances in which subject's participation may be terminated by the investigator without subject consent<br>k. Statement of additional costs to subject that may result from participation in the study<br>l. Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject<br>m. Statement that significant new findings which may related to subject's willingness to continue participation will be provided to subject<br>n. Disclosure of approximate number of subjects involved in the study<br>o. Statement: "A description of this clinical trials will be available on the www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time"<br>p. Statement that a copy of the consent form will be given to the subject<br>• Failure to revise the informed consent document in response to a safety report or Action Letter regarding risks<br>• Significant or substantial changes to the consent form document deviating from the CIRB-approved boilerplate (other than local context) for NCTN/ETCTN studies<br>• Consent form document contains changes not approved by the local IRB, including changes to questions that do not match the model consent form<br>• Multiple cumulative effect of lesser deficiencies for a given consent form<br>• Other (explain) |
| **Lesser Deficiencies** | • Consent missing dates, dated incorrectly, or signatures in the wrong location<br>• Consent missing all required subject responses<br>• For NCTN/ETCTN studies, failure to have the informed consent document (after CIRB amendment approval) locally implemented within 30 days of notification (posted on the CTSU website)<br>• Language/text is missing or added that is administrative or editorial in nature (e.g., rephrasing a sentence/section to add clarity, reformatting the document and/or changes made related to contact information are examples of an editorial or administrative change) |

| | |
|---|---|
| | • IRB approved informed consent document with incorrect version date<br>• Other (explain) |
| **Delegation of Authority Review** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Performing tasks not assigned to individual<br>• Failure to keep DOA current<br>• Individual not listed on DOA<br>• Other (explain) |
| **Lesser Deficiency** | • Other (explain) |
| **Patient Case Review - Informed Consent** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity<br>• Consent form document not signed and dated by the patient/study participant (or parent/legally authorized representative, if applicable)<br>• Patient/study participant signature cannot be corroborated<br>• Consent form not protocol specific |
| **Major Deficiencies** | • Failure to document the informed consent process with the study participant<br>• Patient/study participant signs consent form document containing changes not approved by the CIRB/IRB<br>• Consent form document missing<br>• Translated consent, short form or other form of translation not available or signed/dated by a non-English speaking patient/study participant<br>• Consent form not signed by patient prior to study registration/enrollment<br>• Consent form does not contain all required signatures<br>• Consent form used was not the most current IRB-approved version at the time of patient registration<br>• Consent form does not include updates or information required by IRB<br>• Re-consent not obtained as required<br>• Consent of ancillary/advanced imaging studies not executed properly<br>• Other (explain) |
| **Lesser Deficiencies** | • Dates incorrectly applied<br>• Signatures applied in the wrong location<br>• Consent missing all responses (not otherwise considered major)<br>• Other (explain) |
| **Eligibility** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Review of documentation available at the time of the audit confirms patient/study participant did not meet all eligibility criteria and/or eligibility requirements were not obtained within the timeframe as specified by the protocol<br>• Documentation missing; unable to confirm eligibility<br>• Missing eligibility checklist/verification |

| | |
|---|---|
| | • Tests and/or protocol required procedures to determine eligibility not complete prior to enrollment<br>• Other (explain) |
| **Lesser Deficiencies** | • One or more criteria not explicitly documented in medical or research<br>• Other (explain) |
| **Treatment** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity<br>• Incorrect agent/treatment/intervention used |
| **Major Deficiencies** | • Additional agent/treatment/intervention used which is not permitted by protocol<br>• Dose deviations or incorrect calculations (error greater than +/- 10%)<br>• Dose modification/treatment interventions not per protocol; incorrectly calculated<br>• Treatment/intervention incorrect, not administered correctly, or not adequately documented<br>• Timing and sequencing of treatment/ intervention not per protocol<br>• Unjustified delays in treatment/intervention<br>• Unacceptable frequency of minor violations<br>• Inappropriate administration of non-protocol anticancer treatment (additional drugs, radiation, etc.)<br>• Repetitive or systemic errors in dosing<br>• Repetitive or serious errors in dosing, timing, or schedule<br>• Wrong route in administration<br>• Errors in administering or documenting concomitant medications<br>• Administration of a prohibited medication or treatment<br>• Failure to return unused investigational drug to pharmacy<br>• Failure to perform protocol required safety tests prior to treatment<br>• Other (explain) |
| **Lesser Deficiencies** | • Missing few minor protocol required tests<br>• Wrong antiemetic's/pre-meds given per protocol<br>• Wrong doses (<10% deviation without explanation for one dose)<br>• Wrong timing delay with acceptable explanation (i.e. holiday, bad weather, protocol required delay)<br>• Other (explain) |
| **Disease Outcome/Response** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Inaccurate documentation of initial sites of involvement<br>• Tumor measurements/evaluation of status or disease not performed, not reported, or not documented per protocol<br>• Protocol-directed response criteria not followed<br>• Claimed response (i.e., partial response, complete response, stable) cannot be verified or auditor could not verify the reported response<br>• Failure to detect cancer (as in a prevention study) or failure to identify cancer progression<br>• Other (explain) |

| | |
|---|---|
| **Lesser Deficiencies** | • Minor deviations from the protocol required response assessment schedule<br>• Other (explain) |
| **Adverse Events** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Failure to report or delayed reporting of an adverse event (AE) that would require filing an expedited AE report<br>• AEs not assessed by the investigator in a timely manner (per protocol)<br>• Grades, types, or dates/duration of serious AEs inaccurately recorded<br>• AEs cannot be substantiated<br>• Failure to obtain the required baseline testing necessary to protect subject safety<br>• Follow-up studies necessary to assess AEs not performed<br>• Unreported grade 4 or 5 AEs regardless of seriousness<br>• Recurrent under- or over-reporting of AEs<br>• Recurrent or repetitive issues with proper characterization or grading of events<br>• AEs reported greater than 6 months from the capture date<br>• Other (explain) |
| **Lesser Deficiencies** | • One or two unreported grade 3 AEs regardless of seriousness<br>• Limited underreporting of grade 1 or 2 AEs<br>• AEs reported late but within 6 months of capture<br>• Other (explain) |
| **General Data Management Quality** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |
| **Major Deficiencies** | • Recurrent missing documentation in the patient/study participant records<br>• Protocol-specified laboratory tests not done, not reported or not documented<br>• Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented<br>• Protocol-specified research/advanced imaging studies not done or submitted appropriately<br>• Frequent data inaccuracies<br>• Errors in submitted data<br>• Delinquent data submission (> 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency)<br>• Other (explain) |
| **Lesser Deficiencies** | • Corrections were not handled per GCP guidelines<br>• Other (explain) |
| **Accountability of the Investigational Product** | |
| **Critical Deficiency** | • Any finding identified before or during an audit that is suspected to be fraudulent activity |

| | |
|---|---|
| **Major Deficiencies** | • No documentation for IP accountability<br>• Balance of IP on file does not match physical inventory<br>• IP/device was not used according to protocol and/or was used for other purposes<br>• IP was not stored in accordance with the instructions<br>• IP that expired was used<br>• No records of IP dispensation<br>• No shipping/receiving receipts on file<br>• Temperature monitoring log is not up to date<br>• PI was not destroyed/returned according to the protocol<br>• IP was not kept in a secure place and labeled "investigational"<br>• If a device study, the device was not maintained and disposed in accordance with the IRB-approved plan for device maintenance<br>• No training log for staff<br>• Other (explain) |
| **Lesser Deficiencies** | • The instructions for handling/storage of the IP were not on file<br>• Multiple agents did not have separate records<br>• No documentation of IP dispensation for individual subjects<br>• No procedures in place and followed to ensure that the person prescribing and cosigning prescriptions for IP is an authorized prescriber for the protocol and an order for IP is signed or cosigned by an authorized investigator prior to IP dispensing and administration<br>• Training log is not up to date<br>• Other (explain) |

**Critical Deficiency:** Any condition, practice, process or pattern that adversely affects the rights, safety, or wellbeing of the patient/study participant and/or the quality and integrity of the data. This includes serious violation of safeguards in place to ensure safety of a patient/study participant and/or manipulation and intentional misrepresentation of data (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf).

**Major Deficiency:** A variance from protocol-specific procedures that makes the resulting data questionable.

**Lesser Deficiency:** A deficiency that is judged not to have a significant impact on the outcome or interpretation of the study and is not described as a major deficiency. An unacceptable frequency of lesser deficiencies should be treated as a major deficiency.

## *Appendix D. Summary of Audit Findings (Example)*

**UFHCC QA Department – Summary of Audit Findings**

**Study:** (Insert protocol title here)

**Principal Investigator:** (Insert PI name)

**Audit Date:** (Insert Date here)

**Audit Type:** (Insert audit type here)

**Audit Team:** (Insert names of auditor/auditors here)

**Audit Components:**

| Component | Assessment | FU Required | FU Due Date | Re-Audit Required |
|---|---|---|---|---|
| Regulatory | Not Reviewed | NA | NA | NA |
| Informed Consent | Satisfactory | No | NA | No |
| Drug Accountability | Not reviewed | NA | NA | NA |
| Patient Case Review | Unacceptable | Yes | 09/01/2017 | Yes |

**Informed Consent Review:**

| Subject | Deficiency | Comments |
|---|---|---|
| (Subject initials and numerical identifier here) | Lesser | Consent Documentation – 6/8/2017 MD Note does not cover all required consent items. The following are missing items that need to me addressed:<br>i. Consent was voluntary<br>ii. Subject was given time to read and review consent<br>iii. Subject was given a copy of the informed consent form |

**General Comments:** None

**Regulatory Documentation Review:**

| Category | Deficiency | Comments |
|---|---|---|
| Protocol | None | None |
| FDA documentation | None | None |
| Delegation of Authority Log | None | None |
| IRB Documentation | None | None |
| General Data Quality | None | None |

**Comments:** None

**Subject Case Review:**

| (Subject initials and numerical identifier here) | | |
|---|---|---|
| **Category** | **Deficiency** | **Comments** |
| Eligibility | Major | • Cannot verify several data elements reported as part of the Eligibility criteria in Rave<br>○ Intent for LAR<br>○ Non-bulky diagnosis or not at high risk for metastatic diagnosis.<br>○ If the subject is or is "not a candidate for sphincter-sparing surgery prior to neo-adjuvant therapy".<br>○ No documentation that subject agrees to use adequate contraception.<br>• Noted in RAVE the Clinical N Stage is N2a. Per protocol, nodes do not meet this criteria, please clarify. This is a stratification factor. |

| | | |
|---|---|---|
| | | • Missing signed/dated eligibility documentation. |
| Treatment | Lesser | Unable to verify the treatment for Cycle one was administered. No administration documentation found for 5-fu Bolus Dose 400mg/m2. |
| Disease Outcome/Response | None | None |
| Follow Up | None | None |
| Adverse Events | Lesser | Review recorded AE's in RAVE. Source documentation states the following AE's with the corresponding Grades:<br>i. Diarrhea, Grade 1<br>ii. Nausea, Grade 1<br>Muscle soreness on AE tracking log, but not in RAVE, please update |
| General Data Quality | Lesser | Please ensure that source data (not found within the EMR) is located within the research chart. |

**Comments:**

**General Comments:**

## *Appendix E. Corrective and Preventative Action Plan Template*

**Date:** [Insert date]
**To:** [Insert committee name]
**From:** [Name, title, and institutional affiliation of individual authoring this CAPA, and this individual's signature]

| | |
|---|---|
| **Issue:** | [Brief description of the process of concern which is being documented; may be written in paragraph form or listed out in bullet form.] |
| **Root Cause:** | [The reason(s) that the issue arose.] |
| **Corrective Action:** | [Description of the corrective action taken or planned by the site personnel. If the study team was instructed to perform these corrective actions, indicate whom and the date of instruction.] |
| **Implementation:** | [Description of the procedures used to document resolution of the issue, and the personal who are responsible for these procedures.] |
| **Effective date of resolution:** | [Effective date for the corrective action.] |
| **Preventive Action:** | [Description of the preventive actions taken or planned by study staff. If the study team was instructed to perform these preventive actions, indicate whom and the date of instruction.] |
| **Evaluation/Follow up:** | [Any plan and/or procedures to evaluate the implementation and completion, individuals who are responsible for the evaluations, timeframe for these evaluation(s).] |
| **Comments:** | [Provide any additional comments or information not noted above.] |

_____ _____
Principal Investigator Signature Date of Signature

_____
Principal Investigator Printed Name

## *Appendix F. Audit and Monitoring Log*

**UFHCC CRO Audit and Monitoring Log**

| Protocol OCR#: | IRB#: | PI Name: |
|---|---|---|

**CRO Auditing and Monitoring Log**

| Date(s) of audit | Date of exit interview | Auditor/ Monitor Signature | Type of visit (circle one) | Study Team Signature (at the exit interview) | Comments |
|---|---|---|---|---|---|
| | | | Audit / Monitoring | | |
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