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Introduction

This manual documents policies of the Dana-Farber/Harvard Cancer Center (DF/HCC) Internal Audit System. It also describes the history and the roles of 1) the study team whose protocol is audited, 2) the Quality Assurance Office for Clinical Trials (QACT), 3) the DF/HCC Clinical Investigations Policy and Oversight Committee (CLINPOC), and 4) the Clinical Research Auditors.

The auditing program is a major component of the DF/HCC clinical trial monitoring system. The primary purpose of the audit process described in this manual is to ensure subject safety, verify accurate data collection, identify problem areas, and take corrective action when necessary. This process includes verifying eligibility and protocol and regulatory compliance according to DF/HCC, International Conference on Harmonisation (ICH) Good Clinical Practice and FDA guidelines. Descriptions of preparation, performance, and follow-up for the audit are also included in this manual.

History

The QACT at Dana-Farber Cancer Institute (DFCI) was established in January 1986 to ensure the collection of high quality protocol research data. In 1988, this center developed procedures for the DFCI Internal Audit System to better pursue the goal of maintaining protocol and regulatory compliance as well as complete and accurate data by a peer review system. In 1997, Dana-Farber/Harvard Cancer Center, which now incorporates Brigham and Women’s Hospital (BWH), Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Children’s Hospital (CH), and Beth Israel Deaconess Medical Center (BIDMC), combined audit systems to create a uniform system. Periodically, changes are implemented to increase efficiency and meet the changing needs of the DF/HCC audit system.

Quality Assurance Office for Clinical Trials (QACT)

The QACT sets high standards for data collection and the management of clinical trials, and provides resources to the DF/HCC for the clinical trial process. The QACT performs a variety of functions:

- Prospectively registering all protocol subjects, including consent and eligibility verification
- Monitoring protocol accrual
- Computerizing and monitoring protocol data
- Auditing adult and pediatric DF/HCC protocols
- Assisting investigators with external audits
- Participating in clinical trials process training
- Producing protocol statistical reports
- Coordinating CLINPOC meetings
- Producing protocol flow diagrams
- Producing a computerized protocol system
- Implementing policies as needed for the clinical trial process
- Coordinating the DF/HCC Data Safety Monitoring Committee and Board (DSMC & DSMB)

The department is aligned with the Office for the Protection of Research Subjects (OPRS) and maintains a close association with the Division of Biostatistics and Computational Biology. The QACT derives support from Institute funds, the CORE grant, and other research grants and contracts. In summary, the QACT is a quality assurance and database management resource whose policies and procedures help maintain high-quality protocol management and data.
Clinical Investigations Policy and Oversight Committee (CLINPOC)

The Clinical Investigations Policy and Oversight Committee (CLINPOC) oversees the clinical trial process for the DF/HCC and approves any new policies and procedures implemented by the QACT and the OPRS. CLINPOC was organized in 1986 as a committee to oversee the clinical trial process at the Dana-Farber Cancer Institute including the two departments that manage the clinical trials systems, the OPRS and the QACT. This role expanded in 1999 to include DF/HCC institutions, which gave written agreements for CLINPOC to serve as their oversight and policy committee for clinical trials. The oversight includes: the protocol review process, the functioning of the OPRS, QACT, and Clinical Trial Operations (CTO) offices, the internal auditing program, accrual monitoring, the process for Data and Safety Monitoring and the policy and procedures for the management of clinical trials. CLINPOC meets monthly and is comprised of senior medical staff, with representation from Biostatistics, Research Administration, Nursing, Pharmacy, QACT and OPRS. There are members from DFCI, BWH, CH, BIDMC, and MGH. CLINPOC has three subcommittees including: Audit, Operations and Accrual Monitoring. CLINPOC reports to the Medical Staff Executive Committee (MSEC) at DFCI and through them to the Board of Trustees. The minutes are forwarded to the Chair of the Clinical Research Committee of DF/HCC. CLINPOC is considered a “peer review” committee and is part of the continuous quality improvement mechanism.

Audit Subcommittee

The CLINPOC Audit Subcommittee was formed in 2004 in order to facilitate the review of the DF/HCC internal audit program, to provide clinical input for the audited protocols and identify any needed DF/HCC system changes that may be brought to light through the internal audits.

Meeting Structure & Responsibilities:

The Audit Subcommittee meets monthly to insure timely oversight of internal and external audits and to allow additional time for CLINPOC to address policy issues

The Audit Subcommittee reviews all internal audit reports provided by the clinical research auditors. The subcommittee discusses the protocol audit findings and their grades based on the DF/HCC standardized audit performance evaluation scale. The subcommittee decides when corrective action and/or education are needed to ensure quality improvement.

The Audit Subcommittee reviews summary reports of external audits provided by the QACT to ensure that DF/HCC is aware of audit activity and findings. The Audit Subcommittee will determine if an internal audit or follow-up action is necessary.

The Audit Subcommittee provides a monthly report to CLINPOC of the audits reviewed, the grades given, and any issues that were identified at the last meeting. When the subcommittee determines audit findings of a protocol are unacceptable, the CLINPOC Chair and Co-Chair are notified and can take immediate action if needed. At the next full committee meeting, CLINPOC reviews the audit report and the subcommittee chair reports the findings and recommended actions to CLINPOC. The subcommittee can also refer any major problems that have been identified to CLINPOC. In such cases where the audit findings result in issues of risk to subjects and other regulatory issues, the clinical research auditor will also notify the IRB by sending a memo along with the appropriate report attached to the Director of the OPRS.

The subcommittee oversees the auditing process including the results, methods, reporting and ultimately the educational opportunities. Additionally, the subcommittee has oversight of the auditing program’s impact on the DF/HCC policy and procedures and regulatory compliance. The Quality Assurance Office for Clinical Trials (QACT) manages the administrative tasks of the Audit Subcommittee. This subcommittee is considered peer review protected; therefore, the audit reports are confidential.
**Membership:**
Members and the chair of the subcommittee are appointed by the chair of CLINPOC every two years. Membership includes representation from the DF/HCC institutions, as well as, biostatistics, pharmacy, nursing, the Director of Office for the Protection of Research Subjects (OPRS) and the Director of the QACT.

A quorum consists of a majority of the voting members, including at least one physician.

**How the Audit System Works**

The process begins with the selection of a protocol to audit. The Clinical Research Auditor selects protocols according to set criteria; disease site schedule, prioritization within the disease site, new investigators, and number of subjects accrued.

The Clinical Research Auditor contacts the Principal Investigator (PI) and study team with information to review in preparation for the audit four to five weeks in advance via email. The email contains the audit notification, which describes the audit proceedings and how to prepare for the audit. The email also contains a list of subjects to be audited. During the audit, the Clinical Research Auditor will compare the medical records and research files to the protocol document and submitted forms to verify compliance and accurate data collection.

Throughout the audit, the PI and the study team are available to assist the Clinical Research Auditor as needed. The Clinical Research Auditor completes an audit review form for each subject during the audit to assess performance of data collection and protocol compliance documented in the record. The exit interview usually takes place within 72 working hours of the audit completion. The Clinical Research Auditor leads the exit interview with the PI and study team. During the exit interview, the PI and the study team respond to the findings, recommendations, or questions that have arisen during the audit.

At the exit interview, the Clinical Research Auditor gives a copy of the audit findings to the PI and the study team. In addition, when subject safety issues are observed during an audit, the Clinical Research Auditor sends a copy of the summarized audit findings to the Chairman and Co-chairman of CLINPOC for review. At this point, CLINPOC has the opportunity to take immediate action if deemed necessary. The complete final audit report is then written and signed by the Clinical Research Auditor and mailed to the PI and the study team within two weeks of the exit interview. The PI is asked to sign acceptance of the audit report and reply with corrective action plans as needed. The CLINPOC audit subcommittee reviews the report at the next meeting to determine if further action is required. The audit subcommittee reports the audit reviews monthly to CLINPOC.

*Timeframes listed here are ideal. The timeline may vary per audit.*
Selecting Protocols and Subjects for Audit

Protocol Selection:
Each Clinical Research Auditor selects a minimum of two protocols a month to audit. All active DF/HCC protocols are eligible for audit, including those protocols sponsored by NCI, pharmaceutical industry or other sponsors. The following rubric is used for prioritizing protocols to audit:

- Human gene transfer protocols are audited annually.
- In-house & NCI/NIH funded protocols are audited a minimum of once in their lifetime. Priority is given to high-risk studies. Disease programs are chosen on a rotating basis and a protocol is eligible after five subjects have been accrued, unless the target accrual is less than 10 subjects.
- Industry and Cooperative Group trials: Annually, a minimum of one industry and cooperative group trial will be audited per disease group.
- Affiliate hospitals are audited annually after at least two subjects are entered on trial(s).
- For cause audits of protocols requested by CLINPOC or OPRS including re-audits.
- Protocols identified as fast accruing by the CLINPOC Accrual Monitoring Program (expected duration less than one year or accrual rate is 1.5 times faster than expected).

Each disease site will be audited every three to six months to ensure protocol compliance. An Overall Principal Investigator (PI) who is audited once during the year may be audited a second time during the year on a different protocol.

The Clinical Research Auditor selects protocols from a list of eligible studies and disease sites. The auditor attempts to distribute the audits evenly among the various disease programs and protocols including multimodalities. The three full time DF/HCC auditors will audit approximately 60-70 protocols annually.

Subject Selection:
The Clinical Research Auditor selects five to six subjects to audit from the selected protocol. Subject selection is impartial, taking into account subjects accrued throughout the lifetime of the study and/or the number of affiliate subjects. Subjects should be selected from all participating DF/HCC institutions. Generally, the Clinical Research Auditor reviews five subjects in approximately five days. The subjects are chosen to reflect treatment throughout the life of the protocol. Individual auditors should complete all subjects (100%) selected for the audit.

Scheduling Audits
The Clinical Research Auditor informs the Overall and Site PIs, the appropriate study team members, and the designees of the individual DF/HCC institutions who oversee the data management of the audit at least four to five weeks in advance. The Clinical Research Auditor also schedules the exit interview with the PI and his/her study team. Via email, the Clinical Research Auditor provides the Principal Investigator and study staff with the following:

- A notification letter listing the information that will be audited and the logistics of the week, such as time, date and place
- A list of the subjects to be audited
- A copy of the DF/HCC Clinical Trials Audit Manual, which includes a list of major and minor violations categories

Audit notification of the Principal Investigator of the DF/HCC protocols at affiliate sites follows the same guidelines as those listed above.
Audit Preparation Responsibilities

The Clinical Research Auditor:
Prior to the audit, the Clinical Research Auditor is responsible for the following:

- Review confirmations of registration for each subject from the QACT
- Reviewing the protocol file in the OPRS to make copies and to verify appropriate completion of:
  a) Institutional Review Board (IRB) initial approval
  b) IRB approval of amendments
  c) IRB approval of annual continuing reviews
  d) Current version of the protocol and the informed consent document
  e) Reported adverse events
  f) IRB written approval of the protocol from any affiliate institution involved in the audit
- Contacting the Pharmacy to set up a time to review all records regarding the dispensing of investigational drugs and at least two NCI Drug Accountability Records for review (if applicable)

One or two days before the audit, the Clinical Research Auditor calls members of the study team to confirm the date, time and place, and to answer any final questions.

The Principal Investigator and the Study Team:
Prior to the audit, the Principal Investigator and study team is responsible for the following:

- Gathering all inpatient and ambulatory records for the selected subjects
- Gathering completed case report forms (CRFs) and research files for the selected subjects
- Gathering original eligibility checklists, consents and off-study forms for the selected subjects (if not in charts or files)
- Flagging the required elements of the protocol in the selected subjects charts
  o Refer to the "Eligibility", "Subject Entry" and "Required Data" sections of the protocol. Source documentation should exist and be flagged for all required items.
  o Create a "note-to-file" when there is a discrepancy that requires clarification in the record. Sign and date any note-to-file and include how the information was obtained. (Please note, note-to-files do not replace the need for deviation or violation submissions, when applicable).
- Ensure the regulatory binder is complete and up-to-date (DF/HCC SOP PM-409, Lead Site Regulatory Binder Checklist, Non-Lead Site Regulatory Binder Checklist)
- As the lead site, communicate with other participating sites, which have subjects selected

Audit Visit
The PI and study team are responsible for providing the required medical records, research files, and other documentation at the designated location. The Clinical Research Auditor will review these materials during the audit with the study team available to answer any questions.

The Clinical Research Auditor will complete an audit review form (ARF) for each subject selected. The following elements will be reviewed in the subject’s source documentation and documented on the ARF:

- Informed Consent
- Eligibility
- Treatment
- Adverse events
- Response
- Lab Tests/Study Procedures
- Data Management Assessment
- Other

Refer to Appendix A for a detailed description of each of the ARF elements.
**Exit Interview**

The exit interview will ideally occur within 72 working hours of the completion of the audit. The PI and Site PIs are required to be present during the exit interview. The study team members are also strongly recommended to attend.

The Clinical Research Auditor presents the audit findings and responds to any questions from the PI and study team. It is important at this point to discuss all questionable issues and provide opportunities for clarification. Any missing, incomplete, or incorrect data should be given to the Clinical Research Auditor within one week of the exit interview.

The Clinical Research Auditor will describe the audit reporting and follow-up process at the end of the exit interview. The audit rating will not be determined until after the exit interview.

**Audit Reporting & Review**

**Final Audit Report:**
The Clinical Research Auditor will complete the final audit report within two weeks of the exit interview. The final audit report lists the specifics of the audit, including the dates of the audit, institutional sites, study team members, IRB review findings, pharmacy review findings, a detailed list of major and minor violations, and recommendations.

The Clinical Research Auditor sends a signed hard copy and an email attachment of the completed final audit report to the PI and study team within two weeks of the exit interview. The PI and the study team should review the final audit report and discuss a corrective plan of action as needed.

**Principal Investigator’s Formal Response:**
The PI may be requested to respond in writing to the Clinical Research Auditor regarding the overall findings of the audit using the criteria specified below.

No formal written response will be required if the audit of the protocol is deemed as “Exceptional” (evidence of superior source documentation) or “Satisfactory” (few minor deviations noted). However, a formal written response by the PI is required if the audited protocol is evaluated as “Acceptable, needs follow-up”, or “Unacceptable”. If a formal written response is required of the PI, a maximum of one week is allotted.

**CLINPOC’s Policy for Reviewing Audit Ratings**

**“Exceptional”, “Satisfactory”, or “Acceptable, needs follow-up” Audits:**
For audits evaluated as no less than “Acceptable, needs follow-up”, the CLINPOC Audit Subcommittee will review the final audit report, and if applicable, the PI’s written response at the next scheduled meeting. The Audit Subcommittee’s determinations are summarized and reviewed by the full CLINPOC committee on a monthly basis.

Below are general guidelines for interpretation of major and minor violations:

- Major violations are considered serious and require corrective action by the PI and the study team.
- Minor violations may be expected to occur occasionally. The CLINPOC evaluates the number of such minor violations and observes patterns.

CLINPOC could accept or conditionally accept the audit rating and final report. Conditional approval could require the study team to implement CLINPOC recommendations or require further follow-up.
Further follow-up may involve:

- Implementation of new procedures regarding individual protocol performance or system-wide changes within Dana-Farber/Harvard Cancer Center
- A re-audit of the protocol in question
- Auditing a related protocol if the previously audited protocol is closed
- Temporary closure or suspension of the protocol to accrual or conduct
- Closure/completion of the protocol

The Clinical Research Auditor, as designated by the Chairperson of CLINPOC, will contact the PI of the audited protocol in writing within 3 days of the committee meeting to relay the results of the CLINPOC evaluation.

Feedback will be provided to all clinical research staff about general audit findings through educational sessions sponsored by the Clinical Trial Education Office (CTEO) and Audit Alert emails sent to the research community through the research listserv.

**Unacceptable Audits:**

If an audit is evaluated as “Unacceptable”, the Clinical Research Auditor must notify the voting members of the CLINPOC Audit Subcommittee and the Chair and Co-Chair of CLINPOC of the violations within 48 hours of the exit interview. The notified members must review the major violations and inform the Clinical Research Auditor if they agree with the “Unacceptable” evaluation within 24 hours. If the majority vote for the “Unacceptable” rating, a formal standardized letter from the Chair of the CLINPOC Audit Subcommittee to the PI (with the PI’s Division Chief cc’ed) will accompany the final audit report. This formal letter, sent within 24 hours of the majority vote, will alert the PI of the Audit Subcommittee’s agreement with the audit rating and will instruct the PI to prepare a written response to the major violations outlined in the final audit report within five working days.

If during an audit, a subject safety risk is discovered, the Clinical Research Auditor must notify the voting members of the CLINPOC Audit Subcommittee and the Chair and Co-Chair of CLINPOC of the violations immediately. The members must review the violations and determine an action plan by consensus within 24 hours. Also, the DFCI Quality Improvement, Risk Management and Patient Safety Officers will be notified of any subject safety risks discovered. The DFCI Officers will be responsible for contacting their counterparts at collaborating institutions if applicable.

CLINPOC has the opportunity at this point to take immediate action, including closure of accrual and/or conduct of the protocol, if deemed necessary. Immediate action by CLINPOC would take place in the event of suspected subject safety risks, research fraud, or an extremely deficient audit.

If protocol closure/suspension is deemed necessary, the Chair of the CLINPOC or designated member would contact the PI, Director of OPRS, Director for Research, and those responsible for oversight of the PI of the protocol within 24 hours of the audit finding notification via the phone. These phone conversations must then be documented and given to the Clinical Research Auditor via an email or memo. The Director of OPRS will notify the IRB chairs and will take steps to amend the protocol tracking system and the Oncology Protocol System to reflect the closure. A protocol, which has had accrual suspended because of any serious or continuing non-compliance and has harmed subjects as determined by the IRB, will be reported to the US DHHS Office for Human Research Protections (OHRP) and the FDA, if appropriate. The Director of the OPRS will notify OHRP in writing within 30 days of the IRB’s decision if the serious and continuing non-compliance meets the threshold for a report as set forth in the OPRS policy.

If fraud or extreme carelessness is noted for a DF/HCC protocol, the CLINPOC Chairperson or designated member will notify the Director for Research, the Chair of the IRB and the applicable Division Chief. The CLINPOC Chairperson and the Director for Research may direct the OPRS to immediately close the protocol while an investigation takes place under the Scientific Misconduct Policy in place at the DF/HCC.

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 CLINPOC meeting.
Any protocol closed by CLINPOC can only be reopened after CLINPOC and the DFCI IRB determines the trial should be reopened.

If a PI has two or more “Unacceptable” audits within two years, CLINPOC will send a written request to the PI’s superior requesting a written plan for addressing the concerns of committee raised by the multiple unacceptable audits.

**Appeals Process**

The standard process for an audit review is at the monthly Audit Subcommittee meeting, where the formal PI written response and audit findings are assessed.

In cases where the PI feels that the audit was inaccurate or unfair and wishes to appeal, the PI of an audited study may request to be present during the Audit Subcommittee’s review of the audit. The PI must notify the Clinical Research Auditor of the request to attend the Audit Subcommittee meeting after the final report is received. The PI should prepare and submit to the Clinical Research Auditor a formal written response to the audit findings prior to the scheduled meeting.

At the open session of the Audit Subcommittee review, the PI will have the opportunity to present and discuss their concerns with the subcommittee members. During the closed session, the PI will be required to leave and the Audit Subcommittee will review the issues presented by the PI and make a determination. The PI will be notified of the Audit Subcommittee’s decision within 24 hours of the meeting.

In the event the PI feels the issues have not been addressed adequately, the appeal will progress to the full CLINPOC committee. The PI must notify the Clinical Research Auditor of the request to appeal to the full CLINPOC committee after the audit subcommittee’s decision is received and the appeal will be scheduled for the next scheduled monthly CLINPOC meeting.

The PI will have the opportunity to present and discuss their concerns with CLINPOC during the open session. During the closed session, the PI will be required to leave and CLINPOC will review the issues presented by the PI as well as the Audit Subcommittee’s evaluation and will make a final determination. The PI will be notified of CLINPOC’s decision within 24 hours of the meeting.

**Audit Database**

A database is maintained by the Clinical Research Auditors to provide statistical information that can be used to improve the audit process and to document institutional changes, which have been implemented as a result of the audit findings. This information is presented to the CLINPOC members on a semi-annual basis.
Audit Response & Review:
*Exceptional, Satisfactory, or Acceptable, needs follow-up Audits*

Acceptable, needs follow-up

Satisfactory or Exceptional

PI response required for any major violations detailed in the final audit report

Audit Subcommittee reviews final audit report, audit rating, and PI response (if applicable)

Audit Subcommittee approves

Audit Subcommittee conditionally approves and requires either implementation of recommendations or further follow-up

CLINPOC is notified at monthly meeting
Audit Response & Review:
Unacceptable Audits

Subject safety risk suspected during the audit

Audit Manager immediately notifies the voting members of Audit Subcommittee and Chair and Co-Chair of CLINPOC of the safety concerns

Within 24 hours of notification, CLINPOC determines an action plan and notifies the Audit Manager

Within 48 hours of the exit interview, the Audit Manager notifies the voting members of Audit Subcommittee and Chair and Co-Chair of CLINPOC of the major violations

Within 24 hours of notification, the Audit Subcommittee and CLINPOC Chair and Co-Chair vote to determine Unacceptable rating and notifies the Audit Manager

Immediate action (temporary closure of trial/suspension of accrual) is taken if deemed necessary (subject safety risks, research fraud or extremely deficient audit) and the PI will be contacted and suspension of accrual letter sent

If agreed, unacceptable audit rating letter is sent with final audit report requesting a response to the major violations within 5 working days

Response accepted

Response is not adequate and 2nd response with clarifications required

Response deemed not adequate, forward to CLINPOC for action

Response deemed not adequate, forward to CLINPOC for action

Response accepted

CLINPOC is notified at monthly meeting
Clinical Trial Standards Applied During Audit Proceedings

Major and Minor Violations:
The guidelines below, a compilation of ECOG, CALGB and NCI definitions, were created at the DFCI in July 1994 to help define major and minor violations. An exhaustive list of examples is not given, but the examples are intended to guide the reviewers in assessing and categorizing specific violations. A major violation is generally defined as 1) An infringement, which significantly alters the clinical effectiveness of the treatment or the evaluation of its toxicity, 2) An infringement which violates Federal or DF/HCC requirements or policies or 3) Cumulative minor violations of the same nature. Minor violations are problems that occur when the protocol is not followed exactly, but the data are usable and valid or small deviations from Federal or DF/HCC policies.

<table>
<thead>
<tr>
<th>MAJOR VIOLATIONS</th>
<th>MINOR VIOLATIONS</th>
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<tbody>
<tr>
<td><strong>A. Informed Consent</strong></td>
<td><strong>A. Informed Consent</strong></td>
</tr>
<tr>
<td>- Failure to document properly obtained subject consent or IRB or Sponsor mandated</td>
<td>- Consents do not have date/appropriate signature</td>
</tr>
<tr>
<td>re-consent</td>
<td>- Consents do not have unique subject identifiers on each page</td>
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<tr>
<td>- Consent dated after registration/treatment of subject</td>
<td></td>
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<tr>
<td>- Consent not obtained in a language fully understood by the subject</td>
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<tr>
<td>- Outdated consent used</td>
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<tr>
<td><strong>B. Eligibility</strong></td>
<td><strong>B. Eligibility</strong></td>
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<tr>
<td>- Does not meet eligibility criteria</td>
<td>- Small variations of criteria with reasonable explanation/approval (Phase II and</td>
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<tr>
<td>- Many eligibility criteria not documented in the medical record</td>
<td>III only)</td>
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<tr>
<td><strong>C. Pre-therapy</strong></td>
<td><strong>C. Pre-therapy</strong></td>
</tr>
<tr>
<td>- Pre-therapy tests of major importance were not done or not done prior to</td>
<td>- Missing few minor tests</td>
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<tr>
<td>therapy</td>
<td></td>
</tr>
<tr>
<td>- Unacceptable frequency of minor violations</td>
<td></td>
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<tr>
<td>- Failure to obtain baseline CT scan to document pre-therapy tumor size</td>
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<tr>
<td><strong>D. Registration/Randomization/Stratification</strong></td>
<td><strong>D. Registration/Randomization/Stratification</strong></td>
</tr>
<tr>
<td>- Subject not registered prior to treatment</td>
<td>- Date of birth, date of diagnosis, lab values or dates inconsistent</td>
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<tr>
<td>- Information given at registration is inconsistent with actual data in medical</td>
<td></td>
</tr>
<tr>
<td>records chart (wrong stage, diagnosis, cell type, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>E. Forms/Data Submission/Special Requirements</strong></td>
<td><strong>E. Forms/Data Submission/Special Req.</strong></td>
</tr>
<tr>
<td>- Submission of data outside of protocol /DF/HCC guidelines</td>
<td>- Incorrect data (sporadic pieces of data are incomplete or inaccurate)</td>
</tr>
<tr>
<td>- Incorrect data (substantial amounts of data are incomplete or inaccurate for 1</td>
<td>- Few forms not submitted to QACT</td>
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<tr>
<td>or more forms)</td>
<td></td>
</tr>
<tr>
<td>- Substantial number of forms not submitted to QACT</td>
<td></td>
</tr>
</tbody>
</table>
F. Treatment
- Inappropriate administration of non-protocol anticancer treatment (additional drugs, radiation, etc.)
- Failure to modify doses according to protocol, especially where doses are expected to have a major impact on outcome
- Failure to dose reduce in the face of severe toxicity
- Failure to dose escalate on a dose-intensity study
- Inappropriate dose reduction on a dose intensity study
- Repetitive or systemic errors in dosing
- Repetitive or serious errors in dosing, timing, or schedule
- Wrong route in administration
- Failure to document drug administration
- Error in concomitant medications
- Failure to administer an important medication or the administration of a prohibited medication or treatment
- Failure to return unused investigational drug to pharmacy

G. Toxicity
- Failure to obtain the required protocol baseline studies needed to effectively assess toxicity
- Failure to get necessary follow-up studies to assess toxicity as required by protocol
- Unreported grade 4 & 5 toxicities
- Repetitive failure to report grade 2 & 3 unexpected toxicities
- Serious or repetitive failure to properly characterize toxicity or grade
- Failure to file required NCI Adverse Reaction Reports according to protocol when applicable
- Repetitive failure to report adverse events to FDA and sponsor (depends on reporting requirements)
- Repetitive failure to report IND safety reports to the IRB

H. On-Study Procedures
- Unacceptable frequency of required evaluation violations

I. Response/Follow-Up
- Failure to assess disease status according to the required protocol guidelines either pre-therapy or in response to treatment
- Failure to obtain the required follow-up CT scans/biopsies/tumor markers to define a response as specified in the protocol
- Inaccurate assessment of tumor response
- Substantial inaccuracy in the detection of cancer (as in a prevention study) or determination of cancer progression

J. Data Quality
- Unacceptable level of missing documentation
- Missing charts
- Repetitive failure to obtain protocol specified laboratory tests or diagnostic studies
- Frequent inaccuracies or errors in submitted data

K. Regulatory Requirements
- Unacceptable level of missing documentation in Regulatory Binder
- Failure to comply with Institutional Review Board (IRB) approval and reapproval guidelines, including lapsed or expired annual continuing reviews, inappropriate use of less than full-board review and approval and improper review of appropriate amendments or revisions (i.e. subject entered prior to IRB approval.)

F. Treatment
- Wrong antiemetics/pre-meds given per protocol
- Wrong doses (<5% deviation without explanation for one dose; or 5% deviation from dose reduction indicated)
- Wrong timing delay with acceptable explanation (i.e. holiday, bad weather, flu sx)
Protocol Subject Registration

All subjects must be registered before protocol treatment begins. Subjects not registered to a research protocol before treatment begins are considered ineligible and registration is denied. To expedite the registration and eligibility review process the completed eligibility checklist and entire signed consent document should be faxed to the QACT Registrar. When registration must occur after hours, the registering person calls the QACT registration line before treatment begins to leave a message detailing the registration and eligibility criteria. These subjects are registered remotely.

Non-BMT: Obtain all required baseline tests, scans, etc., and have all results in hand. Lab tests must be completed within 14 days prior to study entry if not otherwise specified in the protocol. Baseline measurements must be documented from tests within 14 days of study entry for protocols requiring measurable disease. Other non-lab tests must be performed within 30 days of study entry.

BMT: Eligibility tests for subjects on BMT protocols must be completed within 42 days of registration – except with regard to cardiac and pulmonary functioning. Subjects for whom such tests show normal results within the previous 6 months and whose transplant dates are delayed may be enrolled on study without having the cardiac and pulmonary tests repeated.

If the protocol states a different time frame other than above, the protocol time frames take precedence. This procedure applies to all clinical protocols involving human subjects with particular emphasis being placed on high-risk studies. Subjects on DF/HCC protocols at affiliate institutions must be registered prior to treatment as described above.

Drug Accountability

NCI and private sponsors require all institutions conducting clinical trials with sponsor-supplied investigational drugs to maintain drug accountability records. The information below describes procedures for drug ordering, drug accountability and drug returns.

The NCI Division of Cancer Treatment (DCT) provides investigational drugs for use in CTEP approved (Cancer Treatment Evaluation Program) protocols to registered investigators with a current 1572 form on file with the Pharmaceutical Management Branch (PMB). Private sponsors also require an investigator to file a current 1572 form. The PI identified on the protocol is the physician under which the investigational drug is ordered and there will be only one PI per site. Affiliate institutions involved with an NCI sponsored trial order their own drug supply. Affiliate institutions involved with a privately sponsored trial arrange drug supply shipments with the sponsor.

Drugs for NCI sponsored trials are ordered through three methods: 1) completing a Clinical Drug Request Form and mailing it to the Data Management and Authorization Section (DMAS), 2) ordering the drug via the Electronic Clinical Drug Request system and 3) faxing a complete order form to DMAS at 301 480-4612. Investigational drugs for privately sponsored trials are ordered as per the sponsor’s instructions.

Drug accountability records must record the receipt, use, and disposition of all investigational drugs. Drug shipping and return receipts as well as correspondences from the sponsor regarding drugs (such as drug expiration dates) are maintained on file.

Any unused or unopened investigational drug is returned to the trial sponsor for destruction unless authorized by the trial sponsor to destroy on site following the institution’s waste handling procedures. The pharmacy department’s quality assurance program includes an indicator and monitor program to ensure investigational drug accountability records are completed appropriately. Selected NCI drug accountability records are audited on a monthly basis. Results of the audit are reported to the appropriate committees according to the Institute’s Quality Improvement Plan.
Audit Performance Scale Guidelines

The following guidelines are used to evaluate the protocol performance found in an audit:

**Unacceptable**
- Number of audit-wide major violations per subjects audited is greater than or equal to 0.6. Formal PI written response required.
  - *or*
  - *or*
- Misconduct or fraud. Formal PI written response required.

**Acceptable, with follow-up**
- Audit with any major violations, which does not fit into the “Unacceptable” definition. Formal PI written response required.

**Satisfactory**
- Few minor violations noted. No formal PI response required.

**Exceptional**
- Evidence of superior source documentation, data quality, protocol compliance and regulatory compliance. No formal PI response required.
### Appendices

#### A. Audit Review Form

The Clinical Research Auditor uses the audit review form as a checklist during the audit. One audit review form is completed for each audited subject.

<table>
<thead>
<tr>
<th>Protocol #</th>
<th>Subject MRN</th>
<th>Date of Review</th>
<th>Audit Mgr</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Informed Consent</strong></th>
<th>Source</th>
<th>Data Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please √ responses appropriately</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Is there a consent form for the subject enrolled?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the consent the correct IRB approved version?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did all the required individuals sign and date the consent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the research staff member who signed the consent approved by the DF/HCC policy?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the subject sign the consent prior to enrollment (and prior to starting study specific tests/procedures)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If subject had to be re-consented, is the informed consent form available for review?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the consent process properly documented for initial consent and any re-consents?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there documentation that a copy of the consent was given to the subject?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the subject registered correctly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Eligibility</strong></th>
<th>Source</th>
<th>Data Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the subject meet all inclusion/exclusion criteria?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were all pre-enrollment activities completed per protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Treatment</strong></th>
<th>Source</th>
<th>Data Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the subject discontinue any protocol-prohibited medication according to protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the correct treatment regimen given?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was study drug dispensed per protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was only protocol therapy given?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the subject dosed properly per protocol?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was the correct treatment schedule followed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was there adequate documentation of treatment, including pre-meds or others?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other (Specify)</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td>Were dose adjustments done per protocol and were the reasons for dose adjustments provided?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Were type, grade, dates/duration, and attribution of adverse events adequately reported?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Were SAE’s reported correctly and within the required time frame per protocol?</td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Was response accurately assessed, documented and recorded per protocol requirements?</td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lab Tests/Study Procedures</strong></td>
<td>Were tests/procedures implemented as approved by the IRB?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Were the labs/procedures for this subject documented in the study records?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If a procedure was missed, was the reason properly documented?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was there documentation of lab specimen collection and storage?</td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Data Management Assessment</strong></td>
<td>Is follow-up being done per protocol for this subject?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Is the data quality complete and acceptable?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Are the research file and clinic chart organized?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was data completed in a timely manner?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was the data accurately recorded on the case report forms?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Was the audit preparation completed according to QACT guidelines for this subject?</td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Were deviations or violations properly documented for this subject?</td>
<td></td>
</tr>
<tr>
<td>Other (Specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**B. Audit Drug Accountability Form**

The DF/HCC Pharmacy Review Form is used to verify proper handling and dispensation of drugs.

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**DF/HCC Pharmacy Review Form**

Protocol Audited: 
Medical Record Audit Date: 
Pharmacy Audit Date: 
Clinical Research Auditor: 
Pharmacy Contact Name:

Type of inventory system used to account for IND agents supplied through the NCI or Pharmaceutical Company for DF/HCC protocols (circle all that apply):

- Manual (NCI drug accountability forms)
- Computerized
- Other (explain)
- None

☐ A separate drug inventory record must be maintained for each protocol.
☐ A separate inventory record must be maintained for each dosage and strength.
☐ Drug order, transfers, and returns must be properly documented.
☐ All receipts must be maintained.
☐ IND agent access must be limited to authorize personnel only.
☐ IND agents must be identified separately by protocol and strength.
☐ Expiration dates must be checked regularly.
☐ If applicable, transfers to and from the satellite location must be documented.

☐ Does the drug log balance match the amount of drug in stock?
☐ Does the quantity of logged drug correspond with amount received by NCI?
☐ Are the drugs in stock in date?
☐ Are the drugs stored according to recommended storage conditions?

Comments:

Subject number and initials: _________________________

Does the information about drug administration in the medical record correspond with the date and amount of drug as recorded in the pharmacy log? ____

Comments:

Subject number and initials: _________________________

Does the information about drug administration in the medical record correspond with the date and amount of drug as recorded in the pharmacy log? ____

Comments:

Subject number and initials: _________________________

Does the information about drug administration in the medical record correspond with the date and amount of drug as recorded in the pharmacy log? ____

Comments:

Subject number and initials: _________________________

Does the information about drug administration in the medical record correspond with the date and amount of drug as recorded in the pharmacy log? ____

Comments:

Are all drug entries clearly legible? ____

Comments: