1. BACKGROUND:

This document describes the Dana-Farber/Harvard Cancer Center (DF/HCC) Internal Audit Program and related procedures. This program is managed by the DF/HCC Office of Data Quality (ODQ) and overseen by the DF/HCC Audit Committee.

All clinical trials conducted at DF/HCC participating institutions are subject to internal audit by the ODQ. Internal audit results are confidential and peer-review protected.

2. ASSOCIATED DF/HCC POLICIES:

2.1. AUD-100

3. PROCEDURE:

3.1. Full Scope Audits

3.1.1. A full-scope audit is a comprehensive review of all clinical research activity under a specific protocol at one or more research locations. A full-scope audit typically involves review of the following by one or more auditors:

- **Regulatory** including but not limited to:
  - Institutional Review Board (IRB) documentation
  - IND status and compliance
  - Adverse event, deviation and violation reporting
  - Study personnel records, delegated tasks, and qualifications
  - Required regulatory documents (e.g., 1572)

- **Pharmacy** including but not limited to:
  - Investigational product accountability records
  - Storage requirements (security, temperature, etc.)
  - Receipt, dispensation, return, and destruction processes and records

- **Subject Cases** including but not limited to:
  - Informed consent
  - Eligibility and registration
  - Treatment and/or study interventions
  - Adverse event, deviations and violations
  - Evaluation of protocol objectives (e.g., response)

- Protocol-mandated tests and procedures
- Data collection (e.g., accuracy, timeliness)

3.1.2. Typically, 4-5 subjects are reviewed during a full-scope audit; however, the number of subjects selected may vary depending on the type and complexity of the protocol. The auditor(s) will routinely request records for at least one unannounced subject during the audit.

3.2. **Process Audits**

3.2.1. A process audit is a systematic review of a specific aspect of the clinical research process across trials, disease programs, and/or research locations. Process audits are intended to identify areas for improvement by evaluating trends in conduct and compliance, both positive and/or negative. Process audits result in summary reporting 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.

3.2.2. The scope of a process audit will vary. For example, an audit may focus on trials of a certain type, trials under specific investigators or research teams, or a scattered sampling of trials across institutions.

3.2.3. The Office of Data Quality uses information from many sources to identify areas for process audit. These sources may include trends observed during the conduct of other internal/external audits and inspections, concerns raised by various oversight committees (e.g., Audit Committee, Data Safety Monitoring Committee (DSMC), Data Safety Monitoring Board (DSMB), Clinical Research Operations Committee (CLINOPS), Clinical Investigations Leadership Committee (CLC), and input from Clinical Trials Offices and DF/HCC leadership.

3.3. **Mock Audits**

3.3.1. A mock audit is an informal audit performed to assist in preparations for a scheduled or anticipated inspection by the Food and Drug Administration (FDA), the National Institutes of Health (NIH), National Cancer Institute (NCI)/Cooperative Groups, or other regulatory authorities. Its primary purpose is to assist the Overall PI in identifying any issues of non-compliance that have gone previously undetected and/or unreported during routine conduct of research activities.

3.3.2. The ODQ's availability to perform a mock audit is dependent on resource availability and scheduling.

3.3.3. The auditor(s) may review any or all of the items typically included in a full scope audit. The ODQ will coordinate with the Overall 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.

3.3.4. The results of the mock audit review are provided to the Overall PI, key members of the study team, and the institutional Clinical Trials Office. If significant non-compliance is identified during a mock audit, the ODQ will share the findings with the Audit Committee, the DF/HCC Medical Director for Clinical Trials Operations and the DF/HCC Associate Director for Administration.

3.4. **Audit Selection**

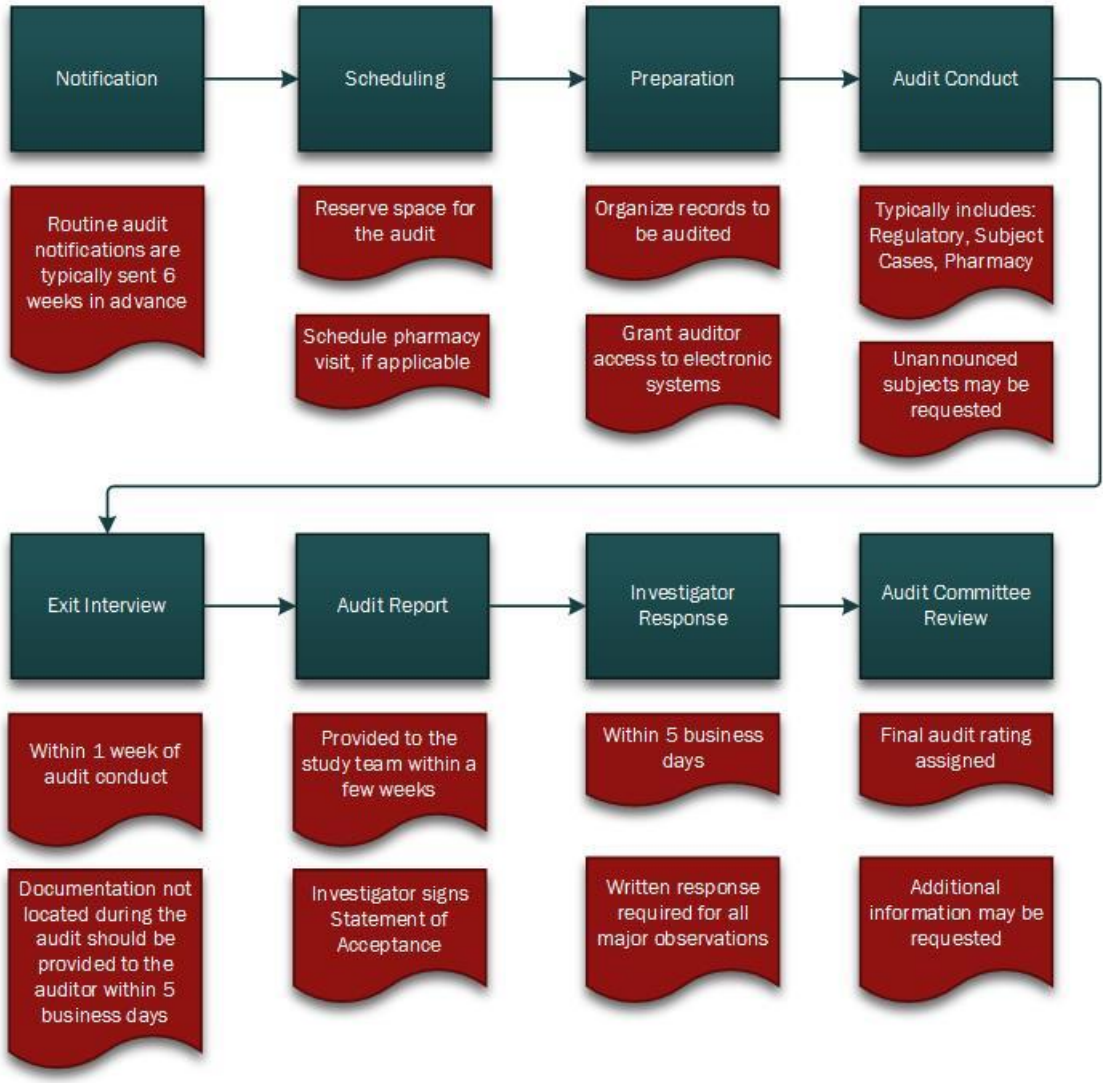
3.4.1. All open DF/HCC protocols are eligible for audit, including those protocols sponsored by the NCI, the pharmaceutical industry or other sponsors. The Office of Data Quality uses a risk-based algorithm to assist in prioritizing protocols, sites, investigators, and study teams for audit. This algorithm considers the following factors:

- Phase and risk (e.g., treatment protocols, human gene transfer protocols)
- Sponsorship (e.g., investigator-sponsored, industry-sponsored, or cooperative group)
- NCI/NIH funded protocols
- Current accrual and accrual rate
- Protocols conducted by new clinical research investigators
- Participation of DF/PCC Affiliate hospitals and the last time each affiliate was audited
- The last time the investigator / institutional disease program was audited on another protocol

3.4.2. Overall PIs may be audited several times a year depending on the size and composition of their research portfolio. Similarly, disease programs conducting large numbers of studies will likely be audited more frequently.

3.4.3. Audits may also be requested by a DF/HCC oversight committee (CLC, IRB, DSMC, DSMB, etc.) or DF/HCC leadership in response to specific observations or concerns.

3.5. **Audit Process**



3.6. **Notification and Scheduling**

3.6.1. The Overall PI and study team will receive six to ten weeks' notice in anticipation of a full-scope internal audit. Notification will be communicated via email. The initial notification will identify a window for the audit to occur (typically ~ 1 month) and include a request that the Overall PI and study team identify options for audit days and space during the audit window.

3.6.2. On site auditing activities are performed during normal business hours and typically completed within one week. Exit interviews generally take place within 3 business days of the completion of audit activities. Whenever possible, the Overall PI is expected to be present for the exit interview. Once the audit schedule and space are set, the ODQ will assign an auditor. The ODQ Audit Manager will need to approve any requests to reschedule audit activities if rescheduling will significantly delay the conduct of the audit or exit interview.

3.6.3. The assigned auditor will confirm the audit schedule and location via email at least 2 weeks prior to the audit start date. This confirmation will include a list of subject cases to be audited and scope of the review. Unannounced subjects, when applicable, will be identified during the on-site review.

3.7. **Preparation**

3.7.1. Prior to the audit, the Overall PI and study team are responsible for gathering and organizing all records in preparation for the audit. While the ODQ does not require study records to be maintained in a specific format or organizational system, 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 Overall PI and study team must plan to have records available to the auditor(s) at the designated audit location.

3.7.2. Auditing of electronic documents is permissible so long as the auditor is provided with appropriate access to the electronic records. The Overall PI and study team must ensure that the auditor will have access to electronic materials at the start of and throughout the audit.

3.8. **Audit Conduct**

3.8.1. The auditor(s) will coordinate with the primary study team contact regarding start and end times each day. Typically, the auditor(s) will request a daily check-in with the study team to discuss the materials reviewed that day and any questions that the auditors need clarification on.

3.8.2. At the completion of the audit, the study team is responsible for retrieving study records from the audit location and/or terminating electronic access, as applicable.

3.9. **Exit Interview**

3.9.1. The exit interview is an opportunity for addressing questions that have come up during the audit, generating suggestions and recommendations for rectifying issues of non-compliance, and identifying strategies for future process improvement.

3.9.2. During the exit interview, the auditor(s) will provide a list of preliminary observations to the Overall PI and the study team. A final report will not be available as this time. The grading of

observations as major/minor for the Final Audit Report will account for information shared during the exit interview and follow-up period; therefore, the auditor(s) will not be able to indicate grading of their observations during the discussion.

3.9.3. If documentation was not located by the auditor during the audit, the study team will be given a short window following the exit interview to demonstrate to the auditor that the documentation was not, in fact, missing. However, the study team is not expected to resolve all discrepancies or concerns during this window. Corrections made after the exit interview will not result in removal of observations from the final audit report.

3.10. Audit Report

3.10.1. The auditor(s) will complete a draft of the Final Audit Report within approximately two weeks of the exit interview. All reports must be reviewed and approved by the ODQ Audit Manager to ensure uniform reporting and quality standards are maintained.

3.10.2. The Final Audit Report identifies the specifics of the audit, including; the dates of the audit, sites audited, detailed observations made by the auditors, and any recommendations from the audit team. Observations will be graded as major or minor per the following definitions (see Appendix A for examples):

- **Major** is used for non-compliance that has the potential to significantly impact the integrity of the study data (e.g., ability to evaluate the effectiveness of an intervention or its toxicity), the safety or rights of study subjects, or clearly violates applicable regulations or DF/HCC policies. In addition, cumulative minor observations that are similar in nature and indicate possible systemic non-compliance may be considered major.

- **Minor** is used for instances of non-compliance that do not significantly impact evaluability or integrity of the data, or the safety and rights of study subjects. Small and infrequent deviations from Federal or DF/HCC policies are also considered minor observations.

3.10.3. In addition, the auditor(s) will assign an overall rating for each audit component (i.e., regulatory, pharmacy, subject cases) per the following criteria:

- **Unacceptable (A formal written response is required)**
  - Multiple major observations within a single component. Typically, this means 2 or more major observations in either the regulatory or pharmacy component, 2 or more major observations impacting more than a single subject case, or 3 or more major observations across all subject cases.

- A single flagrant deficiency (e.g., life-threatening major observation, or a concern for misconduct or fraud)

- **Acceptable, needs follow-up (A formal written response is required)**
  - Multiple minor observations
  - Any major observation
- **Acceptable (No response required)**
  - No major observations
  - Few, if any, minor observations

3.10.4. Upon approval from the ODQ Audit Manager, the auditor(s) will send a signed copy of the completed final audit report via email to the Overall PI, Site Responsible Investigator(s), the respective study teams and the institutional clinical trials office.

3.11. Investigator Response

3.11.1. The Overall PI and/or Site Responsible Investigator always has the opportunity to provide a written response to the audit results. However, a formal written response, signed by the Overall PI, is required for "Acceptable, needs follow-up" or "Unacceptable" ratings.

3.11.2. Investigators are given 5 business days to provide a response unless an extension is requested and approved by the ODQ Audit Manager. Written responses should be submitted along with the signed Statement of Acceptance page.

3.11.3. A written response should include the following components:
- A detailed explanation of the root cause
- A corrective action plan to correct the non-compliance observed by the auditor
- A preventative action plan to decrease the risk of repeated non-compliance in the future.
- Identification of responsible persons for carrying out corrective and preventative actions
- Dates on which corrective and preventative actions were or will be completed

3.11.4. If a protocol amendment is proposed as a result of the audit findings, the PI will be required to submit the proposed amendment with the signed final audit report for review and approval by the Audit Committee before submission to the DFCI IRB.

3.11.5. Responses are not required for Mock Audits.

3.12. DF/HCC Audit Committee Review

3.12.1. The DF/HCC Audit Committee reviews and approves all Final Audit Reports generated by the ODQ. This process is confidential and peer-review protected. Audit ratings of Acceptable require

no further action or response, unless otherwise indicated by the Audit Committee. Audit ratings of Acceptable, with follow up or Unacceptable require a written response from the Investigator addressing all major observations.

3.12.2. The Audit Committee also reviews violations submitted to the IRB. Although previously-reported IRB violations are not considered audit observations, the type, number and reporting timeframe of the violations are considered when determining overall protocol compliance.

3.12.3. The Audit Committee may approve or conditionally accept the audit ratings and final report. Conditional approval indicates that the Audit Committee requires additional information or action from the investigator and study team to conclude their review.

3.12.4. The Audit Committee may request or recommend additional action, including but not limited to:

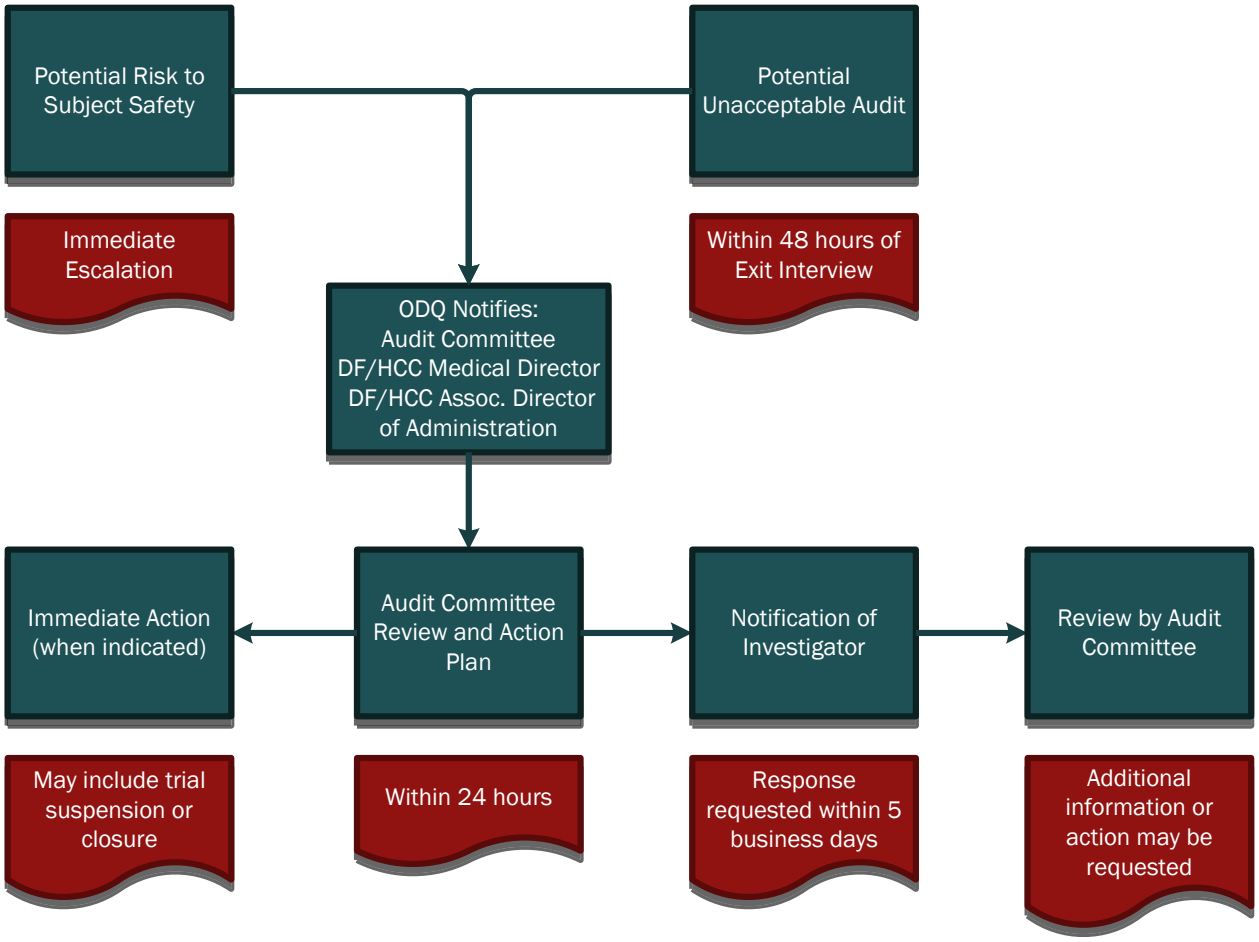
- Additional audits of the protocol or other, related protocols
- Suspension of protocol accrual or protocol closure by the IRB
- Protocol amendment or revision
- Training, education, or mentorship of the investigator or study team
- Policy or process changes within the DF/HCC

3.12.5. The auditor, as instructed by the Audit Committee, will contact the Overall PI of the audited protocol via email within 5 business days to relay the results of the Audit Committee's evaluation.

3.12.6. The CLC reviews the outcome of all DF/HCC Audit Committee meetings.

3.12.7. Documentation of the audit, Audit Committee response and any required follow-up action is maintained in the ODQ Audit files.

3.13. Escalation



3.13.1. Escalation of concerning audit findings may be initiated by the ODQ Audit Manager, ODQ Director, or the DF/HCC Audit Committee. Escalation may occur immediately during the conduct of an audit (e.g., significant safety concerns observed), or as a consequence of reviewing the final audit report. Escalation begins with the DF/HCC Audit Committee, and continues as appropriate to the DF/HCC Medical Director and DF/HCC Associate Director for Administration, and the CLC.

3.13.2. In the event of an Unacceptable audit rating, the ODQ will notify the voting members of the Audit Committee, the DF/HCC Medical Director and the DF/HCC Associate Director for Administration within 48 hours. The Audit Committee will review the observations within 24 hours to confirm the Unacceptable rating and determine the appropriate action.

3.13.3. The Audit Committee has the authority to take immediate action in the event of suspected risk to subject safety, research fraud, or extreme non-compliance, up to and including a recommendation

of temporary or permanent closure to accrual and/or suspension of all research activities to the IRB.

3.14. Appeals Process

3.14.1. If an investigator feels that an audit was inaccurate and wishes to appeal, a formal request can be made to redress the Audit Committee's review. Appeals can only be requested after the Audit Committee has reviewed the final audit report and communicated a final rating to the investigator.

3.14.2. If the Audit Committee agrees to hear the appeal, the investigator, will be notified and invited to attend a meeting with the Audit Committee as soon as schedules allow. In preparation for presenting an appeal, the investigator should submit a formal written response to the ODQ Audit Manager prior to the scheduled meeting.

3.14.3. Appeals begin with an open session period during which the investigator will have the opportunity to present and discuss their concerns with the Audit Committee members. Afterward, a closed session will be held during which the Audit Committee will make a determination.

3.14.4. Within 24 hours of the meeting the PI will be notified of the Audit Committee's decision.

Appendix A: Examples of Major and Minor Observations

	MAJOR	MINOR
Informed Consent	Failure to document properly obtained subject consent or IRB Sponsor mandated re-consent Consent dated after registration/treatment of subject Consent not obtained in a language fully understood by the subject Outdated consent used	Consent missing date or appropriate signatures Consent missing unique subject ID on each page.
Eligibility	Patient does not meet eligibility criteria Eligibility criteria not adequately documented in the medical record Subject not registered prior to start of treatment	Small variations in eligibility criteria with reasonable explanation/approval
CRF Data Compliance	Substantial amounts of data that are incomplete or inaccurate Greater than 50% missing data	Greater than 10% missing data
Treatment	Failure to make dose modifications per the protocol, Repeated, serious or systemic errors in administration of the investigational agent(s) Administration of treatments or procedures prohibited by the protocol. Substantial missing or inaccurate records of administration, accountability, return, etc. Unaccounted for investigational product.	Out of window administration with acceptable explanation Small number of discrepancies in administration or accountability records
Adverse Events and Toxicities	Failure to conduct required study procedures needed to assess toxicities. Failure to report Grade 4 and Grade 5 toxicities within timeframe. Repeated failure to report unexpected toxicities or repeated failure to properly grade Repeated failure to report mandated adverse events to the FDA and the study sponsor. Failure or late reporting of Serious Adverse Events. Failure to grade and assign causality to AEs and SAEs by a study clinician. Repeated failure to review IND Safety Reports within 60 days	Failure to report a single Grade 3 or lower toxicity. Small number of discrepancies in toxicity documentation
Study Procedures	Unacceptable frequency of failure to perform protocol specific evaluations. Repeated failure to obtain protocol specific laboratory tests or diagnostic studies. Failure to perform significant protocol procedures necessary to evaluate toxicity or study objectives	Missing a small number of minor required evaluations or tests.
Study Documentation	Unacceptable level of missing documentation. Missing charts Frequent inaccuracies or errors Misplaced and unrecoverable source documentation	Missing a small amount of required documentation with an acceptable explanation. Small number of errors with corrections. Disorganized study files
Regulatory	Substantially incomplete regulatory binder. Failure to comply with Institutional Review Board (IRB) approval and re-approval guidelines.	Small number of missing regulatory documents Small number of errors with corrections. Disorganized study files