



The George Washington University School of
Medicine and Health Sciences

Internal Monitoring Manual

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ABBREVIATIONS

AE	Adverse Event
CAPA	Corrective and Preventative Action Plan
COI	Conflict of Interest
DISC	Data Integrity and Safety Committee
DOA	Delegation of Authority
DSMP	Data Safety and Monitoring Plan
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GWU MFA	George Washington University Medical Faculty Associates
ICH	International Council for Harmonization
IMV	Internal Monitoring Visit
IIT	Investigator Initiated Trial
IRB	Institutional Review Board
NCI	National Cancer Institute
NIH	National Institutes of Health
OCR	Office of Clinical Research
PI	Principal Investigator
SAE	Serious Adverse Event
SMHS	School of Medicine & Health Sciences

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 iRIS, OnCore, and WCG/Advarra. Studies move into an inactive status once they have been formally closed with the IRB and an approval close-out letter has been issued by sponsor or agency.

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

Clinical Trial: “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.”¹

Monitoring Visit (MV): MVs are conducted to ensure the proper conduction of clinical trials and to verify all proper regulatory laws and regulations are being followed. IMVs can be requested by investigators as a safeguard to verify their clinical trial is operating properly, or can be initiated by the Office of Clinical Research to ensure all regulatory policies and guidelines are being met

Intervention: “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.”²

Investigator Initiated Trial: Any clinical trial that was initiated and conducted by a sponsor-investigator. “An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.”³

¹“ National Institutes of Health (NIH)’s Definition of a Clinical Trial,” NIH Grants & Funding, last modified August 8, 2017, <https://grants.nih.gov/policy/clinical-trials/definition.htm>.

²“National Institutes of Health (NIH)’s Clinical Trial Definition,” National Institute on Deafness and Other Communication Disorders, last modified January 11, 2018, <https://www.nidcd.nih.gov/research/clinical-studies/researchers-professionals/clinical-trials-definition#:~:text=An%20intervention%20is%20defined%20as,behavioral%20processes%20and%20For%20endpoints>.

³“Small Business Assistance: FAQ on Drug Development and Investigational New Drug Applications” U.S. Food and Drug Administration (FDA), last modified on August 1, 2023, <https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-drug-development-and-investigational-new-drug#:~:text=Sponsor%20Investigator%20means%20an%20individual,other%20than%20an%20individual..>

Major Finding: “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.”⁴

Minor Finding: 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.”⁵

Principal Investigator: Principal investigator (PI) refers to the person(s) in charge of a clinical trial or a scientific research grant. The principal investigator prepares and carries out the clinical trial protocol (plan for the study) or research paid for by the grant. The principal investigator also analyzes the data and reports the results of the trial or grant research.⁶ 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. “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.”⁷ ICH Good Clinical Practices (GCP) Guideline.

Research Team Member: Any employee who is conducting clinical research that is NOT the PI or Sub-I. These roles include: Clinical Research Coordinators, Research Assistants, Research Nurses, Registered Dietitians, etc. Research Team members are responsible for the maintenance of study records and conducting research in accordance with GCP and GW standards.

Minimal Risk: “*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests⁸.”

⁴ “Clinical Trials Monitoring Branch (CTMB) Audit Guidelines,” National Cancer Institute (NCI) Guidelines as part of the National Clinical Trials Network, last modified March 2023, https://ctep.cancer.gov/branches/ctmb/training/docs/Patient_Case_Review.pdf.

⁵ “Clinical Trials Monitoring Branch (CTMB) Audit Guidelines,” National Cancer Institute (NCI) Guidelines as part of the National Clinical Trials Network, last modified March 2023, https://ctep.cancer.gov/branches/ctmb/training/docs/Patient_Case_Review.pdf.

⁶ “Toolkit,” National Institute of Health (NIH), last modified 2021, [https://toolkit.ncats.nih.gov/glossary/principal-investigator/#:~:text=Principal%20investigator%20\(PI\)%20refers%20to,paid%20for%20by%20the%20grant](https://toolkit.ncats.nih.gov/glossary/principal-investigator/#:~:text=Principal%20investigator%20(PI)%20refers%20to,paid%20for%20by%20the%20grant).

⁷ “Glossary,” International Council for Harmonization (ICH) E6 1.6 Good Clinical Practice Network, last modified 2018, <https://ichgcp.net/1-glossary>.

⁸ 21 CFR 50.3(k), Food and Drug Administration (FDA)

High Risk: “A clinical trial having one or more of the following attributes:

- Providing a non-routine intervention, i.e., an intervention or non-routine use of an intervention that would not otherwise be provided for the condition under study in the local facility where the study is being conducted
- Administrating an unlicensed product
- Administrating a licensed product for an unapproved indication⁹”

I. INTRODUCTION/BACKGROUND audit

Practitioners of clinical trials have an obligation to take appropriate steps to protect both the integrity of science and human study participants in research studies. The integrity of a data set is a function of the entire process of data recording, collection, analysis, and reporting. Detailed plans and systems are needed to assure protocol adherence for the uniform collection of data. Vigilance to detect honest errors, systematic or random, as well as data falsification, is especially important when conducting clinical trials since independent replication of most trials is not feasible. Quality assurance is any method or procedure for collecting, processing, or analyzing study data that is aimed at maintaining or enhancing their reliability and validity. Quality assurance includes prevention, detection, and action from the beginning of data collection through publication of the results. Special efforts should be made to assure unbiased treatment assignment, adequate assessment of eligibility, compliance with protocol treatment and regulatory requirements, and complete collection of data on the primary outcome measures.

The Office of Clinical Research (OCR) internal monitoring team is responsible for conducting internal investigations of all clinical research conducted at The George Washington University School of Medicine and Health Sciences. Trials are selected for internal monitoring inspection per the guidelines outlined in this manual. All research conducted by GWU SMHS, its schools and any of GWU’s affiliate institutions that fall under its purview (i.e., GWU Hospital) is subject to internal monitoring to conduct quality assurance investigations. Internal Monitoring Visits are not limited to only FDA regulated studies, but can also be done on non-clinical trials.

OCR is committed to providing high quality support for the efficient execution and management of impactful clinical research. The primary purpose of an internal monitoring visit is to evaluate overall study conduct and compliance with the approved protocol, the sponsor’s (if applicable) and institution’s standard operating procedures, current GCP guidelines, and regulatory requirements, as well as a root cause analysis of non-compliance or misconduct that may be discovered within a study.

⁹ “Clinical Trial Applicants—Determine Level of Risk,” National Institute of Allergy and Infectious Disease (NIAID), last modified March 17, 2021, <https://www.niaid.nih.gov/grants-contracts/ct-level-risk#:~:text=NIAID%20defines%20a%20%E2%80%9Chigh%2Drisk,the%20study%20is%20being%20conducted>

IMVs will consist of a review of the essential regulatory documents, informed consent process documentation verification of source documentation of data captured on the case report forms submitted for overall data quality. Study conduct including adverse event reporting, deviations reporting, randomization (as applicable), IP administration and storage (as applicable) and data privacy.

Additionally, IMVs may be used to determine if further information is required to be submitted at the time of continuing review, or if the study needs to be escalated to the Office of Research Integrity and Compliance (ORIC) to conduct an audit. The internal monitoring report will be sent to leadership within the OCR/SMHS and it will be determined if the study may continue to remain active under current practices based on the findings. If the study is industry sponsored and a major finding is discovered during the internal monitoring visit, the research team will be required to share any finding(s) with the study monitor and/or the sponsor of the study. The sponsor will then provide recommendations on how they would like major finding(s) to be addressed. The IMV team will work with the research team in responding to a Corrective and Preventative Action (CAPA) Plan in order to address any deviations from industry and institutional standards of research and prevent it from happening in the future.

The GWU Cancer Center: The GWU Cancer Center will have its own internal monitoring policies and SOPs. However, the OCR maintains the authority to review any clinical research study conducted by the Cancer Center and conduct its own investigation when applicable. The Cancer Center will follow guidelines established by the National Cancer Institute (NCI). The GWCC will submit regular reports to the OCR of their internal findings. The OCR will select one study at random being conducted in the GWCC to inspect.

II. SCOPE

This manual applies to all clinical research, including FDA- regulated and non-FDA regulated studies, conducted at GWU/SMHS/MFA as well as GWU's affiliate institutions that fall under its purview, regardless of sponsorship. A clinical trial is "a prospective study involving human subjects designed to answer specific questions about the effects or impact of a particular biomedical or behavioral intervention; these may include drugs, treatments, devices, or behavioral or nutritional strategies."¹⁰

III. OCR INTERNAL MONITORING TEAM

The OCR Internal monitoring team provides ongoing monitoring for greater than minimal-risk research. IMVs are conducted in accordance with the frequency outlined in this manual. It is possible for studies to be inspected at random as a result of a trigger or request by other research offices. The request will be reviewed and assessed and a determination will be made by OCR staff whether a IMV should be conducted. Routine or random IMVs may be conducted for any clinical trial or study. All clinical investigational activities are performed in accordance with the FDA/HHS regulations and in accordance with ICH GCP Guidelines. Industry Sponsored clinical studies should adhere to the sponsor and/or protocol guideline requirements. The internal

¹⁰ "National Institutes of Health (NIH)'s Definition of a Clinical Trial," NIH Grants & Funding, last modified August 8, 2017, <https://grants.nih.gov/policy/clinical-trials/definition.htm>.

monitoring is also intended to evaluate the effectiveness of current institutional training, education and practices. Findings may prompt modifications in standard operating procedures, policies, or research oversight system activities.

The internal monitoring team has the authority to access research and pertinent clinical records of all patients or participants enrolled in studies that fall under its review. This is done in the interest of current and future participants as well as non-study participants that may be impacted by the results of studies conducted at GWU.

Formal reports summarizing the findings of the IMV with identification of any specific findings warranting a CAPA are provided to the PI and research team members for review and response. Copies of the clinical inspection reports are also provided to the offices mentioned in the Inspection Reporting- Contact Flow Chart (Appendix A).

IV. GW SMHS OCR CLINICAL RESEARCH COMPLIANCE COMMITTEE

The GWU SMHS OCR Compliance Committee systemically evaluates the IMV key findings to help identify any potential clinical or operational barriers to research compliance across the enterprise. The Clinical Research Compliance Committee meets once a month to discuss compliance related components at the university. The group can make recommendations if additional corrective actions are required and if additional education is needed to ensure improvements in quality and research compliance.

Membership

Membership includes representation from GWU MFA leadership and GWU leadership including:

- The Office of Clinical Research (OCR)
- The Office of Research Integrity and Compliance (ORIC)
- The MFA Office of Compliance
- The Office of Ethics, Compliance, and Privacy
- The Office of Human Research
- The Office of General Council (OGC)
- GWU Hospital
- Faculty Representative

Reporting to Institutional Offices: When Department Members will need to be notified and involved

For an Inspection Contact Flow Chart, see *Appendix A*.

OCR is responsible for conducting routine, internal monitoring visits. If during an IMV a major finding is discovered, the OCR will notify the Office of Research Integrity (ORIC) who may choose to conduct an audit of the study. If there is a potential breach of confidentiality, subject information, the covered entity's Privacy Officer will be notified who may choose to conduct their own investigation into HIPAA compliance.

Department	Reasons to be Notified
Office of Clinical Research	Conducts the Internal Monitoring
Office of Research Integrity	Concerns revolving around Conflict of Interest (COI); Research Misconduct, including but not limited to: Inadequate Informed Consent(s) process or documentation, Unlawful Disclosures of Protected Health Information (PHI), HIPAA Breaches or Violations, etc...
MFA Office of Compliance	Disclosures of PHI and any issues relating to billings to payers
The Office of Ethics, Compliance, and Privacy	Government Inquiry; Adverse Actions; Any serious legal issue that can result in litigation; Noncompliance Issues;
Office of Human Subjects Research/IRB	Always notified: internal inspection date, and any relevant findings
Office of General Council	Government Inquiry; Adverse Actions; Any serious legal issue that can result in litigation; Noncompliance Issues; Unlawful use of PHI, Confidentiality; Providing Incentives; Sharing Data with outside Institutions without proper Agreements; Fraud in Data or Publications; Professional Negligence/Malpractice; Billing Fraud; Forged or Falsified Documents; Failure to Disclose Individual/Institutional COI; Failure to Disclose Risks; Failure to follow Conflict Management Plan; Anything that might have to be disclosed to a federal agency
GWU Hospital Compliance	Disclosures of PHI as related to Cerner; if GWU Hospital subjects are affected

V. GENERAL INSPECTION OPERATIONS

The IMV process begins with the selection of a protocol. The internal monitoring team selects protocols according to set criteria, such as risk level as assigned by the Scientific Review and Monitoring Committee (if applicable), having an existing COI management plan, time since last monitoring visit, requests for an IMV, new investigators and/or study coordinators, more frequent occurrences of Adverse Events (AE) and Serious Adverse Events (SAE), and number of subjects accrued. Once the protocols for inspection have been selected the trial is assigned to the internal monitoring team. Assignments are based on the team’s current caseload and individual knowledge base of the assigned protocol.

The lead of the internal monitoring team will contact the PI, research team, and department chair via email with an initial IMV notification and a document request letter for preparation of the

inspection approximately 2 weeks in advance of the IMV. The email will contain the inspection notification, which describes the IMV proceedings, how to prepare for the IMV, and a list of documents that will need to be available for inspection. During the IMV, the internal monitoring team ensures data quality by comparing source documentation to the data entered onto the case report forms. The monitor verifies compliance with protocol and regulatory requirements as well as the accuracy of data collection. A member of the research team will work with the internal monitoring team if there is data that needs to be reviewed in an electronic data capture (EDC) system. Access to sponsor systems will be assessed on a case by case basis.

It is important that a member of the study team to be available during the IMV to assist the internal monitoring team as needed. Following the IMV, the internal monitoring team will conduct an exit interview with the PI and research team, together. During the exit interview, the PI and research team will have an opportunity to verbally discuss the findings, recommendations, or questions that have arisen during the IMV. In situations where missing documents have been identified, the PI and study team will be given 2 business days to produce the requested documentation.

A Final Report of IMV findings will be sent via email within 14 business days following the exit interview. The PI will be asked to acknowledge receipt of the report and will be given 30 days to respond to each finding to the OCR and IRB, if applicable, via email. The Office of Clinical Research with assistance from the Compliance Committee, if needed, will then assess the PI’s response to determine if further action is necessary. The Follow-Up Report will also be shared with the IRB, Vice - Dean of SMHS, the Chief Clinical Research Officer, and the Department Chair.

The Cancer Center will be inspected once a year following the same aforementioned steps. The Cancer Center will be required to submit internal monitoring findings at the cadence by which they conduct internal monitoring. The OCR will file the findings from the Cancer Center. One (1) Cancer Center study will be inspected once a year that meet the requirements outlined in section VI.

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

VI. PROTOCOL SELECTION

Protocol Prioritization	Audit Frequency	Criteria to be Selected
Investigator Initiated Prospective Studies	At minimum, four IIT will be inspected/audited each year	<ul style="list-style-type: none"> Likelihood of external agency audits or monitoring. Conducting human subject research involving interactions/interventions without IRB approval

Externally Sponsored Studies	At minimum, two externally funded studies will be inspected/audited each year	<ul style="list-style-type: none"> • Non-disclosure of Conflict of Interest • Conducting non-exempt human subject research without IRB approval • Improper Disclosures of PHI • HIPAA Breaches and Violations • Missing Signed HIPAA Waivers, if applicable
New PIs or Study Coordinators	Once one subject has been enrolled	<ul style="list-style-type: none"> • Missing critical study agreements ie., Data Sharing Agreements • Missing signatures on study documents by appropriate research personnel • Improper maintenance of study regulatory binder
Cancer Center	At minimum, once a year	<ul style="list-style-type: none"> • Improper documentation of required training(s) • Incomplete or unused Delegation of Authority Log (including improper delegation of roles) • Missing research team member qualifications • Drug Dispensing Errors • Improper Use of or Missing Investigational Product • Enrolling a subject who did not meet the inclusion/exclusion criteria, resulting in increased risk of harm • Failing to obtain/ document informed consent • Allowing IRB approval to expire and continuing research activities during the period of expiration • Major research protocol deviations that may place participants at risk from research procedures • Failure to obtain IRB approval prior to recruitment and involvement of human subjects • Inadequate or non-existent procedures for the informed consent process <ul style="list-style-type: none"> • Inadequate supervision for research procedures • Failure to follow recommendations made by the IRB <ul style="list-style-type: none"> • Failure to report adverse events or unanticipated problems to the IRB • Failure to report protocol changes

		<ul style="list-style-type: none"> • Failure to report protocol deviations • Multiple minor noncompliance issues
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**Each PI may be internally investigated several times a year depending on the size and composition of their research portfolio. Similarly, programs conducting large numbers of studies will likely be inspected more frequently.

VII. SUBJECT/PARTICIPANT SELECTION

The internal monitoring team will have access to all participants’ charts, medical records, case report forms (CRFs) during the IMV. The internal monitoring team can review all of the participant records, or they can choose some at random. To maintain the highest quality of protocol-specific research data, subject records will be inspected thoroughly for informed consent process documentation, eligibility criteria, SAE and AE reporting and ALCOA source documentation.

VIII. INTERNAL MONITORING VISIT SCHEDULING

A scheduled IMV date will be set for a time that is mutually convenient for both the internal monitoring team and the research team. The lead monitor will notify the study PI and the primary study coordinator of pending IMV approximately 2 weeks in advance. The lead monitor will communicate the IMV process via email and will include the following:

- A full inventory of items to be inspected
- Logistics, including the date, time, and location of the IMV
- A request for exit interview scheduling

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 INTERNAL MONITORING VISIT

Prior to the IMV, the PI and research team are responsible for gathering and organizing all records in preparation for the IMV. It is expected that the internal monitoring team 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 research team must plan to have records available to the internal monitoring team at the designated location. If there are electronic documents, it is the responsibility of the PI and research team to ensure that the internal monitoring team is granted access throughout the IMV process.

The Internal Monitoring Visit Team

Prior to the IMV, the Internal Monitoring Team is responsible for the following:

1. Review of subject accrual information which includes new subjects enrolled, previously enrolled subjects, and completed (fully reviewed) subjects.
2. Review of the protocol regulatory files to verify/request availability of:
 - a) IRB initial submission and approval
 - b) IRB submission and approval of amendments
 - c) IRB submission and approval of continuing reviews
 - d) The current and approved version of the protocol and informed consent document as well as all previous versions
 - e) Reported AEs/SAEs
 - f) IRB written approval of the protocol from any affiliate institution involved in the inspection/audit, if applicable
3. Review of prior inspection/audit records and findings, if applicable
4. The monitoring team will email the PI or a member of the research team to confirm the date and location of the IMV and to indicate whether any documentation is missing. This will give the study team an opportunity to find this documentation for the IMV.

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

The Principal Investigator and Research Team

Prior to the IMV, the PI and research team are responsible for the following:

1. Gathering all subjects medical records related to the conduct of the trial (if applicable), or grant EMR access to the internal monitoring team
2. Gathering completed data collection forms or case report forms and research files for subjects
3. Obtaining access to required electronic data capture systems that the inspection team will need to use when verifying source documentation in advance of the teams arrival (e.g., REDCap, OnCore or other data reporting tools) OR conduct an over the shoulder review.
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, informed consent documents, and any study related forms for the selected subjects
6. Ensuring all source documentation is available to the Internal Monitoring Team
7. Creating documentation to address discrepancies that require clarification for the research record (e.g., Note to File)
8. Ensuring the investigator site file (i.e., regulatory binder) is complete and up-to-date
9. Ensuring that the following study-related and subject-related documentation is present (as applicable):
 - a) All IRB records, such as all protocol and informed consent document 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 informed consent documents, all documentation for study- related visits, procedures, results, AEs, serious AEs (SAEs), and deviations
 - c) Any important communications with subjects or sponsor (if applicable)
10. Ensuring all requested records and documentation are delivered to the designated IMV location.

PLEASE REFER TO XVIII. APPENDICES

Appendix B. Study Documentation IMV Checklist

During the Internal Monitoring Visit

The PI and research team are responsible for providing access to the required medical records (if applicable), research files, and other documentation. The internal monitoring team will contact the PI or research team members during the IMV to attempt to resolve any questions that may arise. The internal monitoring team will complete a review of all regulatory, pharmacy (if applicable), and subject documentation. The exit interview with the PI and research team will be conducted following the conclusion of the IMV.

X. INTERNAL MONITORING VISIT AND ASSOCIATED PROCEDURES

IMV Procedures

IMVs are conducted to ensure the proper conduction of clinical trials and to verify all proper regulatory laws and regulations are being followed. IMVs can be requested by investigators as a safeguard to verify their clinical trial is operating properly or can be initiated by the OCR to ensure all regulatory requirements are being met.

Reviewed During the IMV

1. Regulatory (may include, but not limited to)
 - a) Documentation of initial IRB submission and approval
 - b) Documentation of Continuing Review submission and approval
 - c) Documentation of IRB submission and approval for all amendments and revisions
 - d) Documentation of SAE/Unanticipated Problem 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 document
 - h) Completed delegation of authority (DOA) logs, if applicable
 - i) Completed training logs
 - j) Investigational new drug or exemption documentation, as applicable
 - k) Essential Documents
 - l) CITI GCP and Biomedical Investigators Training
 - m) Clinicaltrials.gov problem records (as applicable)
1. Subject Records (may include, but not limited to)
- a) Informed Consent Document
 - b) Eligibility evaluation
 - c) Registration
 - d) Treatment
 - e) Product 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 Auditing Team's discretion)
3. Pharmacy (may include, but not limited to)
- a) Product inventory records, including orders, transfers, and returns
 - b) Temperature control logs
 - c) Investigational product expiration dates
 - d) Pharmacy Manual, if applicable
 - e) Training logs

A formal Follow-up report summarizing the findings of IMV will be provided to the PI for review and response. A copy of the formal audit report will also be provided to the Department Chair, Dean of Clinical Research, and the IRB.

XI. INTERNAL MONITORING VISIT FINDINGS

Once the internal inspection is complete, the internal monitoring team will conduct an exit interview with the PI and research team to discuss preliminary findings. The internal monitoring team member will generate a complete follow-up report of their findings. All reports will be viewed and approved by the Office of Clinical Research, and will be transmitted to the IRB. Final reports will be distributed to the PI, the primary study coordinator, and the Vice Dean of SMHS. If findings require a CAPA, the IMV team will work with researchers on how to develop one.

Finding Evaluation	Criteria	
Exceptional	<p>Complete source documentation, outstanding data quality, protocol compliance and regulatory compliance demonstrated. No major violations.</p> <ul style="list-style-type: none"> • No major violations • ≤1 lesser violations per audited study • PI acknowledgement via email required 	
Minor Findings	<ul style="list-style-type: none"> • No major violations • ≤3 lesser violations per audited case • PI acknowledgement required 	
Satisfactory-needs follow-up	<ul style="list-style-type: none"> • One or more major violations (ratio of major findings to reviewed cases <0.5) • Four to 6 lesser violations per each case reviewed • PI response and CAPA plan required 	
Recommend Suspension	<ul style="list-style-type: none"> • Critical or major violations (ratio of major findings to reviewed cases ≥0.5) • A single life-threatening major violation on a subject case • A single major violation that questions the PI's available to conduct research per established regulations and policies • Excessive lesser violations (>6 per reviewed case) • Misconduct or fraud • PI response and CAPA plan required. 	<p>All protocols requiring immediate action or have major findings will be sent to the ORIC for</p>

review. ORIC has the authority to conduct a for-cause or not-for cause audit on the study. It will be communicated to the PI and research team members following the completion of the IMV that the study will be escalated to another office. For any potential breaches of subject confidentiality, the covered entity's Compliance and Privacy Officer will have to investigate for any potential HIPAA violations.

XII. MAJOR AND MINOR FINDINGS

Major and Minor deficiencies are determined per GCP guidelines. The following are general guidelines for interpreting major and minor deficiencies:

- Major findings are considered serious. They require corrective action by the PI and study team. *See Appendix D*
- Minor findings are expected to occur occasionally. The OCR will evaluate the number of lesser deficiencies to observe for any patterns. *See Appendix D*

If a subject safety risk is discovered during an IMV, the internal monitoring team must notify the IRB, ORIC, and Vice Dean of SMHS immediately. The members must review the violations to determine if the IMV results should be submitted to the OHR and ORIC for expedited review. They can recommend immediate action to the PI, such as suspension of enrollment and/or conduct or suspension of the protocol, if it is deemed necessary. Any recommendation to suspend or terminate a study will be determined by OHR and the convened IRB committee and will be communicated directly to the PI. Immediate action by the aforementioned staff 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 research team to provide feedback and to address any questions that may have arisen during the IMV. 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 internal monitoring team will review a list of preliminary observations with the PI and research team. A final report will not be available at the exit interview. The grading of findings as major or minor 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 internal monitoring team during the scheduled IMV, the research team will be given a short window (72 hours) following the exit interview to get this documentation to the Internal Monitoring Team. The research 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 report and listed as resolved on the final report. It is recommended and encouraged that research team members participate in discrepancy resolution during the exit interview whenever possible.

XIV. IMV RESPONSE REVIEW AND SUBMISSION

A Follow-up Report detailing the initial audit findings and any recommendations by the OCR internal monitoring team will be submitted to the PI, primary study coordinator, and Department Chair within 14 business days following the IMV. The Follow-Up Report will also be shared with the offices listed in Appendix A. The PI will have 1 business day to acknowledge the

report. The PI and research team have 30 days to address the findings, if required, for the IMV. If there are major findings, the Office of Research Integrity and Compliance will be notified and a for-cause audit may be conducted. If the PI fails to provide a response within the allotted time frame or the response is inadequate, then the OCR may recommend study suspension to the OHR/IRB until an acceptable response is received, or terminated, per the discretion of the IRB and Vice Dean

XV. CORRECTIVE AND PREVENTATIVE ACTION PLAN

Errors in the conduct of research may occur despite best efforts from the research team. Errors may include deviations from the IRB approved study plan or noncompliance with applicable research regulations or policies. Whether the result of human oversight or process deficiencies, such errors should be identified and when appropriate, the steps taken to resolve them, and to ensure they do not happen again, should be well documented in the research records.

What is a Corrective And Preventative Action (CAPA) plan

A CAPA Plan is a series of measures, to correct the immediate problem, to determine the cause(s) of the problem, and to develop and implement a plan to prevent the problem from recurring. Developing an effective CAPA Plan requires analysis and problem-solving skills and should represent a collaborative effort by the members of the study team. CAPA Plans should be followed through completion and should be monitored by the study team for their success in preventing recurrence of the problem. The entire process should be documented, and this documentation should be maintained as part of the research record.

How to develop and document a CAPA Plan

See Appendix C for a CAPA template.

This template is designed to incorporate the steps described below, but should be modified as needed to capture additional steps taken by the study team and/or specific departmental processes.

The following activities should be included in the CAPA Plan:

1. Describe the identified problem and how it was discovered.
2. Determine whether the problem should be promptly reported to the IRB.
3. Conduct a Root Cause Analysis (RCA).
 - a) RCA is a process of inquiry that is necessary to identify the source of a problem so that it can be effectively resolved and prevented. There may be multiple causes that contribute to a problem and multiple methods to resolve each cause. The root cause is the most basic cause of a problem that may trigger a chain of additional causes.
 - b) The RCA process is most effective when conducted with a team of people to help with brainstorming. It is important to talk to all people involved in the initial

problem and to ask objective, open-ended questions in order to eliminate assumptions and pull together only facts about why a problem occurred.

- c) There are multiple methods by which Root Cause Analysis (RCA) can be conducted, including the following commonly used models:
 - i) Gilbert’s Behavior Engineering Model (BEM) – a performance measurement tool to evaluate six key areas of potential deficiencies or contributors to a root cause. Potential contributors are categorized as organizational/environmental factors (subclassified as expectations and feedback, tools and resources, and consequences or incentives) and personal/individual factors (subclassified as knowledge and skills, staff capacity and qualification, and motives or preferences).
 - ii) The 5 W’s – an approach to clearly identify what happened in relation to additional details including where, when, and why the event happened, along with who was involved in the event’s occurrence in an effort to pinpoint the root cause.
 - iii) The 5 Why’s – an iterative or progressive method of “digging deeper” into an event by repeating the question “Why?” after each possible cause to ensure the ultimate root cause is identified. The answer to each “Why?” forms the basis of the next question. Of note, the question may need to be repeated more or less than 5 times, or may need to be replaced with “Why did the process fail?” in order to successfully identify the root cause. When the last answer ultimately identifies a broken process or a process that does not exist, you may have reached the root-cause level.
 - iv) Fishbone Diagram (Cause and Effect Method) – a graphic technique to help visually identify and display potential causes of a problem and their relationship to each other. Potential causes may be grouped under the classic model categories of Materials, Methods, Equipment, Environment, and People, or the RCA participant group may come up with their own major categories as a starting point.
 - d) Document the RCA process (including maintaining the group’s notes taken during the process) and record the ultimate root cause.
4. Determine what corrective actions should be taken to correct the immediate problem.
- a) Depending on the identified problem, corrective actions might include consultation with and/or reporting to the study sponsor, PI, or IRB, specific actions with a study participant (e.g., reconsent or other notification, additional follow-up or monitoring, or discontinuation/withdrawal), or correction of erroneous data.
 - i) Notes to File in the Participant’s Study File should be used to explain why such actions were taken.
 - b) Record the planned corrective actions including who will complete them, and when they will be completed.
 - c) As the corrective actions are completed, evidence of their completion should be maintained with the CAPA Plan. Examples might include items such as copies of

email correspondence with the study sponsor, copies of corrected study documentation, copies of IRB submissions, and/or explanatory Notes to File.

5. Determine what preventive actions should be taken to prevent the issue from occurring again.
 - a) Depending on the identified problem, preventive actions might include training on research policies or related topics, development of checklists or other tools, development of new processes, revision of study materials, or sequestering of outdated materials (e.g., from active folders into archive folders).
 - b) If study materials need to be revised, an IRB submission may be necessary
 - c) Also, consider the magnitude of the problem identified from the RCA.
 - i) How will you prevent the problem from affecting all subjects in the study?
 - ii) How will you prevent the problem from affecting other studies conducted by the PI or within a department?
 - iii) What processes and procedures will prevent this problem from recurring?
 - d) Record the planned preventive actions including who will complete them, and when they will be completed.
 - e) As the preventive actions are completed, evidence of their completion should be maintained with the CAPA Plan.
 - i) Examples might include copies of new checklists or SOPs, training materials and/or training logs, copies of IRB submissions, or copies of email communication sent amongst the study team to notify them of the changes.
6. Determine and record who is responsible for implementing, assessing, and closing the CAPA Plan.
7. Implement the CAPA Plan and monitor its progress.
 - a) Record any changes to the plan that occur prior to implementation.
 - b) Record when actions were completed and who completed them.
8. Assess whether the CAPA Plan worked and make changes, if needed.
 - a) This is to identify potential recurrences of the problem.
 - b) If the CAPA Plan did not prevent recurrence, revisit the RCA documentation to determine if the true root cause was ever identified. Often, when a CAPA Plan is ineffective, it is because the true root cause of the problem was not identified.
 - c) Document the assessment process and the outcomes of the assessment.
9. Close-out the CAPA Plan.
 - a) Confirm the completion of the CAPA Plan and document the CAPA Plan as complete or closed.

- b) Document the process and any discussions that took place to come to this determination.

XVI. MAINTENANCE OF INTERNAL MONITORING VISIT INFORMATION

Internal Monitoring Visit Findings Tracker

All data from the completed clinical investigation(s) will be entered into an IMV Findings Tracker by the Office of Clinical Research internal monitoring team. The tracker is used to track IMV findings at an institutional level to be able to address any potential areas for improvement. The report must be retained for five years.

Internal Monitoring Reports

All data and information collected from the IMV will be stored on an encrypted shared drive that is only accessible by the Office of Clinical Research Internal Monitoring Team. No access to the shared drive will be granted without the expressed knowledge/approval of the OCRs Executive Director.

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. 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.

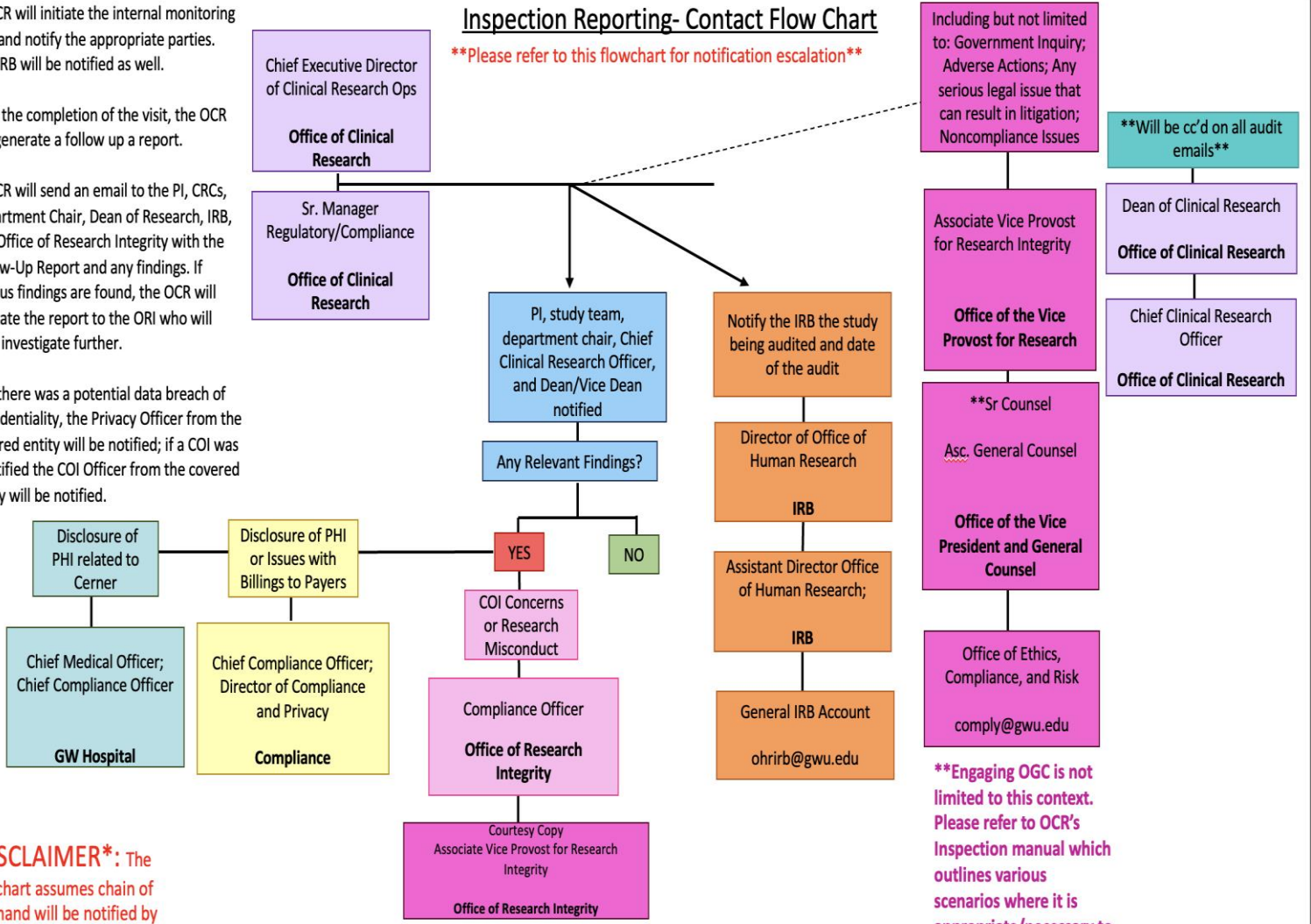
XVIII. APPENDIX

Appendix A. Inspection Reporting- Contact Flow Chart v1.0

Inspection Reporting- Contact Flow Chart

****Please refer to this flowchart for notification escalation****

1. OCR will initiate the internal monitoring visit and notify the appropriate parties. The IRB will be notified as well.
2. At the completion of the visit, the OCR will generate a follow up a report.
3. OCR will send an email to the PI, CRCs, Department Chair, Dean of Research, IRB, and Office of Research Integrity with the Follow-Up Report and any findings. If serious findings are found, the OCR will escalate the report to the ORI who will then investigate further.
4. If there was a potential data breach of confidentiality, the Privacy Officer from the covered entity will be notified; if a COI was identified the COI Officer from the covered entity will be notified.



***DISCLAIMER*:** The flow chart assumes chain of command will be notified by Office representative

****Engaging OGC is not limited to this context. Please refer to OCR's Inspection manual which outlines various scenarios where it is appropriate/necessary to engage counsel.****

Appendix B. IMV Preparation Checklist

IMV Preparation Checklist

In preparation for the IMV have you...	
<input type="checkbox"/> Yes	Identified a key staff member who will be the primary point of contact for the audit team?
<input type="checkbox"/> Yes <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	All research team members have reviewed all the activities for the study under investigation? Protocol Review Subject Enrollment Delegation of Study Procedure
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified all research team members have protocol training for the original protocol and for every subsequent amendment to the protocol (if applicable)
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Located all Protocol Signature Pages, signed and dated by the PI, if applicable?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified the Investigational Brochure is present as well as any amendments made to it, if applicable?
<input type="checkbox"/> Yes	Verified that all research team members have completed any additional trainings required by the sponsor, if applicable?

<input type="checkbox"/> N/A	
<input type="checkbox"/> Yes	<p>Verified all research team members, past and present, are listed on the Delegation of Authority Log and have been delegated the proper roles with respect to their qualifications and signed off and dated by the Principal Investigator (PI)?</p>
<input type="checkbox"/> Yes	<p>Verified all research team members have been IRB approved and staff that are no longer on the study have been removed?</p>
<input type="checkbox"/> Yes	<p>Verified that all research team members have an updated CV that is signed and dated within the last 2 years?</p>
<input type="checkbox"/> Yes	<p>Verified that all research team members have Good Clinical Practice CITI training that is within expiration?</p>
<input type="checkbox"/> Yes	<p>Verified the PI, all Sub-Is, Research Nurses, or Research Pharmacists have a professional license that is within expiration?</p>
<input type="checkbox"/> Yes	<p>Verified the Initial IRB submission and Initial IRB approval letter are filed in the regulatory binder?</p>
<input type="checkbox"/> Yes	<p>Verified any subsequent IRB submissions and approval letters have been filed? (e.g amendments, modifications or staff changes)</p>
<input type="checkbox"/> Yes	

<input type="checkbox"/> N/A	Verified any ads/recruitment or patient facing materials have been IRB approved, if applicable?
<input type="checkbox"/> Yes	Verified that all Informed Consents (ICF) are IRB approved and that all subjects have signed the correct approved version?
<input type="checkbox"/> Yes	Verified all subjects who are participating in the study have a signed ICF?
<input type="checkbox"/> Yes	Verified all ICFs are stored in a secure location?
<input type="checkbox"/> Yes	Located copies of Standard Operating Procedures (SOP) that have to deal with human subject research? I.e., Subject Consenting, Storage of research records, Adverse Event Reporting, IP Storage ect..)
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified a HIPAA Authorization Waiver was included in the ICF and signed by the subject if research pre-screening has taken place?
<input type="checkbox"/> Yes	Verified the subject screening and enrollment logs are correct and up-to-date and securely filed?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified any protocol deviations have been have been documented in a Protocol Deviation Log?
<input type="checkbox"/> Yes	

<input type="checkbox"/> N/A	Verified any Adverse Events have been documented in an Adverse Event Log and any Serious Adverse Event has been documented and reported to the sponsor and IRB?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified any Data Safety Monitoring Board (DSMB) reports have been filed in the regulatory binder?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified any monitoring confirmation letters and follow-up reports have been filed in the regulatory binder, if applicable?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified the FDA 1572 is accurately filled out and signed by the PI, if applicable? (Needs to be updated anytime there is a change in Sub-Is, PI, research locations, labs and IRB)
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified the Investigational Product (IP) Log is up-to-date and accurate, if applicable?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Temperature logs for the location where IP is stored for the duration of the study, if applicable?
<input type="checkbox"/> Yes <input type="checkbox"/> N/A	Verified any chain of custody logs are completed and filed, if applicable
<input type="checkbox"/> Yes	Verified all source documentation is filled out correctly and present?

<input type="checkbox"/> Yes	Verified all regulatory documents are kept securely in a binder?
<input type="checkbox"/> Yes	Located any important correspondences?

Appendix C. Corrective and Preventative Action Plan (CAPA) Template

Study Details	
Principal Investigator:	
IRB Number / Sponsor Number:	
Study Title:	
Responsible Party: <small>(person responsible for overseeing the CAPA Plan)</small>	<p>The following individual, designated by the PI, is responsible for documenting the Problem, Root Cause, and CAPA Plan, updating/revising the Plan as applicable, tracking the CAPA Plan’s completion, and verifying that appropriate documentation related to its completion is included, where applicable, in the study files:</p> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="width: 45%; text-align: center;"> <hr style="border: 0; border-top: 1px solid black; margin-bottom: 5px;"/> Printed Name of Responsible Party </div> <div style="width: 45%; text-align: center;"> <hr style="border: 0; border-top: 1px solid black; margin-bottom: 5px;"/> Responsible Party Role </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 20px;"> <div style="width: 45%; text-align: center;"> <hr style="border: 0; border-top: 1px solid black; margin-bottom: 5px;"/> Responsible Party Signature </div> <div style="width: 45%; text-align: center;"> <hr style="border: 0; border-top: 1px solid black; margin-bottom: 5px;"/> Date </div> </div>

Problem and Root Cause	
Description of	<i>Describe the problem including when and how it was identified. Note policy and/or</i>

Problem	<i>regulations that should have been followed.</i>
IRB Reporting Requirements <i>Refer to GWU HRPP Policy on Reportable Events</i>	<p>_____ Yes, problem should be promptly reported to IRB If yes, date reported to IRB: _____ No, problem does not meet prompt reporting criteria</p> <p>Additional notes: <i>Include any additional notes pertaining to whether the problem is promptly reportable to the Reviewing IRB and/or GWU as an institution.</i></p>
Root Cause Analysis (RCA) Process	<i>Document the RCA process including when and how the process took place and who was involved. Refer to the RCA Information and Tools handout for more information on this step.</i>
Ultimate root cause	<i>Describe the ultimate root cause of the problem identified during the RCA process.</i>

Corrective and Preventive Actions

List all corrective actions	Individual Assigned to Complete the Action	Proposed Date of Completion	Actual Date of Completion

List all preventive actions	Individual Assigned to Complete the Action	Proposed Date of Completion	Actual Date of completion

--	--	--

CAPA Plan Resolution	
Assessment	<i>Describe how the CAPA Plan will be and/or was assessed for effectiveness, including when the assessments took place, who was involved, what decisions were made and why.</i>
Closeout	<i>Describe the process to arrive at closure, including discussions and/or meetings that took place to come to this determination, when they took place and who was involved.</i>
PI Attestation <small>(to be completed when CAPA Plan is closed)</small>	<p>As Principal Investigator, I attest to the completion of the CAPA Plan and confirm that it is considered closed at this time.</p> <p>_____</p> <p>PI Signature Date</p>

Appendix D. IMV Findings Reference Chart

IRB History Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent • Initial approval by expedited review instead of full-board review • Expedited re-approval for situations other than approved exceptions • Registration and/or treatment of patient prior to full IRB approval • Re-approval delayed greater than 30 days, but less than one year • Registration of patient on protocol during a period of delayed re-approval or during a temporary suspension • Missing re-approval • Expired re-approval • Some study staff is not approved by IRB • Internal reportable adverse events reported late or not reported to the IRB • Unanticipated problems, Serious Non-Compliance and/or Continuing Non-Compliance (per OHRP) problems not reported • 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 • 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

	<ul style="list-style-type: none"> • Several missing documents • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • Protocol re-approval delayed 30 days or less • Delayed re-approval for protocol closed to accrual for which all study participants have completed treatment, if applicable • Amendment/Investigator Brochure editorial or administrative in nature or other relevant document not submitted in a timely fashion to the IRB • Few missing documents • Other (explain)
Regulatory Documentation Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent • No 1572 (when applicable) or Investigator Agreement (when applicable) • 1572 (when applicable) signatures are missing • No approved investigational new drug or exempt letter • No Financial Disclosures or some are missing • Several missing documents • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • IB or device manual are not on file • No package insert or product information on file • Not all appropriate investigators are listed on the 1572 • CVs of investigators are not updated, signed or dated (within the last 2 years) • Other (explain)
Informed Consent Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent • Missing any of the following statements or language specific to the elements required per the federal regulations, when appropriate; <ol style="list-style-type: none"> a. Involves research, purposes; duration of participation; description of procedures; identification of experimental procedures b. Description of foreseeable risks or discomforts c. Description of any benefits to subjects or others d. Disclosure of alternative procedures or treatments e. Description of the extent of confidentiality of records f. Explanation regarding compensation and/or whether treatments are available if injury occurs, including who to contact if injury occurs 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 h. Statement that participation is voluntary; refusal to participate involves no penalty or loss of benefits; subject may discontinue participation at any time i. Unforeseeable risks to subject, embryo or fetus j. Statement that circumstances in which subject's participation may be terminated by the investigator without subject consent k. Statement of additional costs to subject that may result from participation in the study l. Statement of consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject m. Statement that significant new findings which may related to subject's willingness to continue participation will be provided to subject n. Disclosure of approximate number of subjects involved in the study

	<ul style="list-style-type: none"> 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” p. Statement that a copy of the consent form will be given to the subject <ul style="list-style-type: none"> • Failure to revise the informed consent document in response to a safety report or Action Letter regarding risks • Consent form document contains changes not approved by the local IRB, including changes to questions that do not match the model consent form • Multiple cumulative effect of lesser deficiencies for a given consent form • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • Consent missing dates, dated incorrectly, or signatures in the wrong location • Consent missing all required subject responses • 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 • Other (explain)
Delegation of Authority Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent • Performing tasks not assigned to individual • Failure to keep DOA current • Individual not listed on DOA • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • Other (explain)
Subject Facing Informed Consent Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent activity • Consent form document not signed and dated by the patient/study participant (or parent/legally authorized representative, if applicable) • Patient/study participant signature cannot be corroborated • Consent form not protocol specific • Failure to document the informed consent process with the study participant • Patient/study participant signs consent form document containing changes not approved by the WCG/CIRB/IRB • Consent form document missing • Translated consent, short form or other form of translation not available or signed/dated by a non-English speaking patient/study participant • Consent form not signed by patient prior to study registration/enrollment • Consent form does not contain all required signatures • Consent form used was not the most current IRB-approved version at the time of patient registration • Consent form does not include updates or information required by IRB • Re-consent not obtained as required • Consent of ancillary/advanced imaging studies not executed properly

	<ul style="list-style-type: none"> • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • Dates incorrectly applied • Signatures applied in the wrong location • Consent missing all responses (not otherwise considered major) • Other (explain)
Eligibility Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent activity • 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 • Documentation missing; unable to confirm eligibility • Missing eligibility checklist/verification • Tests and/or protocol required procedures to determine eligibility not complete prior to enrollment • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • One or more criteria not explicitly documented in medical or research • Other (explain)
Adverse Events Review	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent activity • Failure to report or delayed reporting of an adverse event (AE) that would require filing an expedited AE report • AEs not assessed by the investigator in a timely manner (per protocol) • Grades, types, or dates/duration of serious AEs inaccurately recorded • AEs cannot be substantiated • Failure to obtain the required baseline testing necessary to protect subject safety • Follow-up studies necessary to assess AEs not performed • Unreported grade 4 or 5 AEs regardless of seriousness • Recurrent under- or over-reporting of AEs • Recurrent or repetitive issues with proper characterization or grading of events • AEs reported greater than 6 months from the capture date • Other (explain)
Minor Findings	<ul style="list-style-type: none"> • One or two unreported grade 3 AEs regardless of seriousness • Limited underreporting of grade 1 or 2 AEs • AEs reported late but within 6 months of capture • Other (explain)
General Data Management Quality	
Major Findings	<ul style="list-style-type: none"> • Any finding identified before or during an audit that is suspected to be fraudulent activity • Recurrent missing documentation in the patient/study participant records • Protocol-specified laboratory tests not done, not reported or not documented • Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented • Protocol-specified research/advanced imaging studies not done or submitted appropriately • Frequent data inaccuracies • Errors in submitted data

	<ul style="list-style-type: none"> Delinquent data submission (> 6 months delinquent is considered a major deficiency; a 3- 6 month delinquency is considered a lesser deficiency) Other (explain)
Minor Findings	<ul style="list-style-type: none"> Corrections were not handled per GCP guidelines Other (explain)
Accountability of the Investigational Product	
Major Findings	<ul style="list-style-type: none"> Any finding identified before or during an audit that is suspected to be fraudulent activity No documentation for IP accountability Balance of IP on file does not match physical inventory IP/device was not used according to protocol and/or was used for other purposes IP was not stored in accordance with the instructions IP that expired was used No records of IP dispensation No shipping/receiving receipts on file Temperature monitoring log is not up to date PI was not destroyed/returned according to the protocol IP was not kept in a secure place and labeled “investigational” If a device study, the device was not maintained and disposed in accordance with the IRB-approved plan for device maintenance No training log for staff Other (explain)
Minor Findings	<ul style="list-style-type: none"> The instructions for handling/storage of the IP were not on file Multiple agents did not have separate records No documentation of IP dispensation for individual subjects 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 Training log is not up to date Other (explain)

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

Minor Finding: 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 finding. An unacceptable frequency of lesser deficiencies should be treated as a major finding.