Research Compliance Audit/Quality Review Plan

I. ***Purpose***

The purpose of the Research Audit/Quality Review plan to provide a systematic risk based verification process that ensures that human subject research conducted at the University of Maryland, Baltimore is compliant with federal, local, state and institutional requirements, and promotes human subjects protections through the ethical conduct of research. The Research Compliance Audit /Quality Review Plan fulfills the mission of the Human Research Protections Compliance Program.

II. ***Objective***

The objective of the Quality Review Plan is to provide the UMB research community (Research Investigators, Study teams, IRB and its supporting staff) with an internal system that ensures quality of research conducted, promotes process and quality improvements, and provides practical support through education and training.

III. ***Authority and Scope***

The Research Compliance Audit Plan will be executed under the general direction of the Institutional Official (IO) and in collaboration with the Executive Director/Administrator of the Human Research Protections Program. Responsibilities will be shared among multiple entities within UMB, including the compliance and monitoring groups within the UMB HRPO and the Office of Accountability and Compliance (OAC).

IV. ***Types of Review/Audits***

Random Scheduled Reviews/Routine Audit

This review/audit is either a full audit (100%) or selected audit (5-10%), and will focus on the roles and responsibilities of research team members, regulatory and IRB compliance, consent form elements, recruitment, eligibility and consenting process, case report forms (CRFs) for protocol adherence, source documentation and data collection verification, adverse events(reportable/serious adverse events and non-reportable), data storage and access, drug/device accountability, sample storage and other relevant aspects of the research study.

Random Unscheduled Reviews/Spot Audit

This type of review will focus on a defined aspect of the research conduct including but not limited to review of regulatory documents, recent AE/SAE submissions and modifications, informed consent documentation, eligibility criteria, follow-up reviews from corrective action plans, and data confidentiality and file security.

For Cause/IRB Initiated/IO Initiated Reviews/Audit

This review/audit is initiated out of concerns of noncompliance that may result in an increased risks to participant safety or well-being, infringements of the rights of participants, or questions with regards to the integrity of research data. This type of audit is usually directed by the IRB or the Institution Official in response to these concerns. The review will focus on all aspects of the research including but not limited to the roles and responsibilities of research team members, regulatory and IRB compliance, consent form elements, recruitment, eligibility and consenting process, case report forms (CRFs) for protocol adherence, source documentation and data collection verification, adverse events (reportable/serious adverse events and non-reportable), data storage and access, drug/device accountability, and sample storage. The review will encompass 10% of enrolled participants unless directed otherwise.

Follow-up Audit

This type of audit is occurs when a research study has previously been audited and corrective actions were required as a result of the audit. A follow-up audit is a focused on reviewing corrective actions that were implemented in response to previously identified problems. During the review process, corrective actions and implemented controls must be evaluated to ensure effectives (no reoccurrences of previously identified deficiencies). Follow-up audits may be directed by the IRB to occur within a specific time frame following the initial audit. When warranted, these audits may occur with limited advanced notice.

Post-Approval Monitoring Assessment

This type of review provides an opportunity to educate investigators and research staff on federal, state, local laws, and institutional policies in the areas of research record keeping and study management. It involves a self-assessment completed by the principal investigator (PI) or other knowledgeable study member. Completed Post-Approval Monitoring Assessments may be selected for source document verification (SDV) which may be conducted during an onsite visit or by submissions through secure (21CFR11, HIPAA compliant) methods.

Quality Review

This review is directed by the Institutional Official or Executive Director/Administrator of the Human Research Protections Program and is focused on evaluating the effectiveness and efficiency of a research program. It usually involves performing a quality assessment using a risk based approach and identifying potential risks, and opportunities for improvement as detailed in the Quality Assurance Assessment Plan for the Human Research Protection Office (HRPO). Results and recommendations are submitted to the Institutional Official and other members of leadership as directed.

V. ***Audit/Review Selection***

Audit selection is based on level of risk, category or type of research being conducted and will be selected at random.

Random Scheduled Reviews/Routine Audit/Post Approval Monitoring Assessment:

The following will be reviewed routinely (non-exclusive list):

- Active Investigator-sponsored studies
- Phase I or first in human use studies
- Studies for which the investigator holds the IND(Investigational Drug) or IDE(Investigational Device Exemption)
- Studies without identified oversight, i.e., National Institutes for Health (NIH)
- Investigator with large number of protocols

- High enrollment studies
- Investigator and/or study personnel request
- Significant Risk Device Studies
- High risk studies reporting no adverse events or unanticipated problems
- Studies involving vulnerable populations (employees/students, cognitively impaired, pregnant women/fetuses/neonates, prisoners, children or as identified in 45CFR46 subparts C and D)
- Follow-up of corrective actions resulting from previous audits/reportable new information
- Institutional Review Board (IRB) requested studies
- Approved studies relying on External IRBs
- Approved Studies at external Institutions/Organizations relying on UMB IRB [Including but not limited to- Veterans Administration (VA) Research and Development Committee, and the University of Maryland Medical Center Greenbaum Cancer Center (UMMUC-GCC)]
- Clinical Trials
- Consent process observations
- Studies that no longer require Continuing Reviews based on the changes made to human subject research federal regulations.

Random Unscheduled Reviews/Spot Audit

The following are circumstances where unscheduled reviews/spot audits may occur (non-exclusive list):

- Investigator Initiated Audit
- IND/IDE pre-audit
- New/inexperienced Investigator/research staff

For Cause/IRB-HRPO Executive Director Initiated/IO Initiated Reviews/Audit

Conducted at the request of the IRB (IRB Chair, HRPP Executive Director)/Institutional Official, the following are circumstances where a For-Cause Review may occur (non-exclusive list):

- A complaint received from UMB Hotline-Ethics Point, research participant, family member of participant, or research staff;
- Investigator reported event (Reportable New Information) in which risks to participants have increased due to an action or inaction from the study team;
- Concerns regarding whether the rights and welfare of participants enrolled in research are adequately protected;
- Concerns about the validity/integrity of data collected/allegations of research misconduct directly associated with research participants;
- A History of non-compliance by a particular investigator or research group;
- Verification from sources other than the investigator that unapproved changes have occurred since the previous IRB review;
- Numerous or significant reportable events;
- To support the IRB's assessment of potential non-compliance including failure to follow the approved protocol; and

- Loss of IRB approval secondary to protocol expiration.

Quality Review

The following quality reviews are conducted at the request of the HRPP Executive Director/Institutional Official

- Internal IRB Operations reviews:
  - Review process for Exempt and Expedited studies;
  - Review of greater than minimal risk protocols for appropriate review, IRB processes, adequate consent document content and HRPO Operations activities;
- Quality control review of IRB minutes to determine adequate documentation of meeting discussion has occurred and criteria for approval are appropriately documented;
- Review of department or entity scientific and feasibility review of research of IRB submissions;
- Review of protocols with declared conflicts of interest to ensure proper management of conflict and adequate documentation of conflict;
- Review of research team educational requirements;
- Expertise required for IRB review and the IRB Roster; and
- Verification of IRB approvals for collaborating institutions or external performance sites.

VI. *Audit/Review Scheduling*

Written notification of an upcoming audit will be sent to the Principal Investigator and a copy of the notification is sent to the Chair of the Department/Division, IRB Chair, and HRPO Executive Director. The Principal Investigator is expected to respond and schedule the visit after the notification has been received.

The following is an estimate of the timeframe for notification depending on the type of audit being conducted:

- Routine audits will be scheduled 7 to 14 days in advance;
- Spot audits will be scheduled 5 to 10 days in advance;
- For cause/directed audits may be performed without notice or within 24 hours' notice if there is concern for safety of participants;
- Consent process observations audits may be scheduled by mutual convenience (availability of Auditor/participant being enrolled); and
- Quality reviews are ongoing/scheduled as directed by the IO or HRPO Executive Director.

VII. *Audit/Review Elements*

The following items will be reviewed during an audit/review (non-exclusive list):

Research Study Conduct:

- Protocol Adherence (violations/deviations)
- Informed consent process
- Recruitment and compensation practices
- Sample Storage
- Document Storage/Record retention practices
- Data destruction and Security
- Report submission practices (timely submissions)
- Study data records transmission procedures
- Data and Safety Monitoring Board and Plan (if required)

Research Documentation:

- Source Documentation [original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)].
- Informed consent documents
- Regulatory Binder [screening/enrollment log, Drug/Device Accountability log, Curriculum Vitae of research team members, IRB approvals/communications, current and previous versions of protocol and consent documents, Investigator qualification documentation, product brochure, FDA approvals/communications, financial disclosures, Sponsor communications, training log, site initiation log, local clinical cab certificates/reference ranges, delegation log]
- Unanticipated problems involving risks and adverse events documents
- Modifications/amendments
- Case Report Forms
- Clinical Site Monitoring Visits/Monitor reports

<u>Regulatory/Institutional Compliance:</u>

- Training/Qualification Verification [CITI training, HIPAA training, GCP training for NIH funded studies, Human Subject Research training]
- Conflict of Interest Management Plan (when applicable)

<u>Quality Review Elements:</u>

- CICERO protocol applications
- EC Review summaries
- Pre-reviews, Initial reviews, and Continuing reviews
- Expedited, Exempt, Full Board determinations
- HRP Checklists, Worksheets
- IRB Convened Meeting Minutes, Determination letters
- Quality/Risk Assessments performed
- OAC IRB Written Procedure SOP Checklist

VIII. ***Audit/Review Reporting***

Audit/Review observations/findings will be submitted to the Auditee (e.g. Principal Investigator), the HRPO Executive Director, the IRB Chair and the Institutional Official.
The report will include:
Executive Summary
Observations/Findings
Recommendations/Corrective Action Plan

IX. ***Recommendations/Corrective Action Plan***

Based upon audit/review findings, monitoring results, investigations or other instances of identified deficiencies or non-compliance, corrective action plans may need to be implemented. The following steps are recommended when developing a corrective action plan:
<u>1. Identify the root cause [root cause analysis]:</u>

a. Identify the problem.
b. Identify those impacted as well as those who may have been responsible for the problem. Have discussions (if applicable/feasible) with both groups to better classify the issues contributing to the act(s) leading to the problem identified. It is important to assess whether the rights, welfare, and safety of research subjects were impacted.
c. Questions that are useful in the identification process:
1. What happened? What is the problem?
2. Why and how did the problem occur? What were the steps?
3. Who was affected by the problem? Was it one subject or all subjects in the study?
4. What is the magnitude of the problem? Is it in one study or does the problem exist in all studies under this PI or even in an entire clinical department?
5. Keep asking "why" and "how" until you reach the root cause

Once the root cause has been identified, the next step is to develop a corrective and preventive action plan to eliminate the root cause.

2. Develop a corrective and preventive action (CAPA) plan.

Most regulatory agencies, and institutions conducting research support the theory that the most effective way to resolve problems and non-compliance occurrences in human subject research is to develop a corrective action plan. Although at UMB, investigators have implemented CAPAs for a long time, it is now the expectation that CAPAs are thoroughly documented, implemented and evaluated over time for effectiveness.

Corrections are the immediate steps taken to correct/resolve the problem. These steps may vary depending on the identified problem. However, actions intended to remove any risk of harm or further harm to the research subject must be prioritized first.

Corrective actions are steps taken to remove the root cause of an existing undesirable issue/problem. Corrective actions may include additional reporting that is required (IRB, Sponsor etc.). When issuing reports, ensure that the information provided is accurate and detailed. Some reporting requirements may include a detailed summary of actions taken to prevent further harm to research subjects.

Preventive actions are steps taken to ensure that the problem does not reoccur (i.e. prevent occurrence). Preventive actions may include but is not limited to the following:

- Additional training/education for the principal investigator (PI) and/or research team members
- Development of standard operation procedures (SOPs) designed to prevent occurrences
- Modification(s) of research protocol or procedures
- Modification(s) of the consent processor consent document
- Providing additional information to current, future and/or past research subjects
- Reconfirming consent of current research subjects
- Providing additional follow-up visits/monitoring
- Adding more resources to support research activities

Additional requirements for CAPAs

CAPAs must be SMART:

- Specific-must address the root cause (as it relates to noncompliance-Institutional policies, regulations, sponsor requirements etc.).
- Measureable-must demonstrate that the steps taken were adequate to address the root cause.

- Aligned-must target all parts of the process that led to the root problem.
- Realistic-must be achievable with available resources, knowledge and expertise.
- Timely-must be implemented in a time frame that corresponds to the urgency, importance and seriousness of the problem and impact.

CAPAs must be implemented and documented.

CAPAs must be evaluated over time to verify its effectiveness. If the CAPA has not addressed the root cause (i.e. if there is reoccurrence of the problem), amend the CAPA. Implement the corrected CAPA, document and re-evaluate.

X. *Applicable Regulations, Institutional Policies*

21 CFR 50 – Protection of Human Research Subjects
21 CFR 54 – Financial Disclosure by Clinical Investigators
21 CFR 56 – Institutional Review Boards
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
21 CFR 812 - Investigational Device Exemptions
45 CFR 46 – Protection of Human Subjects
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811
International Conference on Harmonization – E6
UMB HRPP Plan
UMB Research Compliance Program Plan
UMB Investigator's Manual
UMB and USM Policies [https://www.umaryland.edu/spa/policies-and-procedures/umb-and-usm-policies/]

XI. *Revisions*

Date	***Description***	***Author***
Version 10/2018	Original Version	
Revised 10/2020	Updated HRPO Director to HRPO Executive Director	