McLaren HEALTH CARE		**Policy Title:**	Directed For-Cause Audits
Effective Date:	October 8, 2015	**Policy Number:**	MHC_RP303
Review Date:	October 8, 2015	**Section:**	Human Research Protections Program
Revised Date:		**Oversight Level:**	Corporate
Administrative Responsibility:	Corporate Director, HRPP Institutional Official, HRPP		

1. Purpose

1.1. The purpose of this policy is to establish the process for the EQuIP Office to perform a Directed For-Cause Audit of MHC research studies.

2. Scope

2.1. This policy applies to all industry sponsored, government funded, and investigator initiated studies conducted at McLaren Health Care and any of its subsidiaries.

3. Definitions

3.1. Allegation of Non-Compliance: An unproved assertion of non-compliance.

3.2. Continuing Non-Compliance: A pattern of non-compliance that indicates a deficiency likely to result in further non-compliance or circumstance in which an investigator fails to cooperate with investigating or correcting non-compliance.

3.3. Corrective Action Preventative Action Plan (CAPA): A systematic plan to align research conduct in line with federal regulations, laws, and institutional policies.

3.3.1. Corrective Action is the action taken to eliminate the causes of an existing non-compliance issue or other undesirable situation in order to prevent recurrence.

3.3.2. Preventative Action is action taken to eliminate the cause of a potential non-compliance or other undesirable situation in order to prevent occurrence.

3.4. Directed For-Cause Audit: An in-depth examination of any or all components of a research study including, but not limited to all records, documents, observation of processes and interviews with investigators, research staff team members and participants for the purpose of

determining if the rights and welfare of participants are being upheld according to federal regulatory requirements, laws, and HRPP policies.

3.5. Education and Quality Improvement Program (EQuIP): A program that encompass the HRPP Offices of Research Compliance and Quality Improvement with the Office of Education, Training, and Resources.

3.6. Good Clinical Practice (GCP): Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of the trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

3.7. Minor Non-Compliance: Any non-compliance that is not serious or continuing. The non-compliance does or did not:

3.7.1. Harm or pose an increased risk to a participant,

3.7.2. Result in a detrimental emotional or clinical change in the participant or

3.7.3. Have a substantive effect on the value of the data collected.

3.7.4. Examples of minor non-compliance may include, but are not limited to, lapses in continuing IRB approval, failure to obtain a prospective exempt determination from the IRB, minor changes in or deviations from an approved protocol, or administrative error.

3.8. Non-Compliance: Failure to follow the regulations, or the requirements or determinations of the IRB.

3.9. Serious Non-Compliance: Non-compliance that adversely affects the rights and welfare of subjects.

3.10. Refer to Appendix I "Definitions" for additional definitions.

4. Policy

4.1. As part of the McLaren's AAHRPP Quality Improvement and Quality Assurance Program, the Office of Research Compliance and Quality Improvement, through EQuIP, is authorized to perform a directed for-cause audits requested by the IRB, IRB Chairperson, designee, Institutional Official, or regulatory agency (e.g. FDA, NIH, and OHRP).

4.2. McLaren's HRPP is committed to a consistent, proactive effort to continually ensure the human subject research conducted at McLaren occurs in accordance with all applicable federal regulations and/or agency

specific requirements, state and local laws, and institutional policies and procedures.

4.3. Directed for-cause audits of MHC research studies will be conducted:
- 4.3.1. To determine if the rights and welfare of research participants have been properly protected in accordance with federal regulations, local and state laws and institutional policies.
- 4.3.2. To ensure the highest degree of research standards are being maintained in regards to the safety of human subject research.
- 4.3.3. When there are suspicions or allegations of non-compliance.
- 4.3.4. When there are concerns about whether or not the rights and welfare of participants enrolled in a particular research protocol are being adequately protected.
- 4.3.5. When there are concerns about the integrity of the data or research staff misconduct.

4.4. The EQuIP staff has the right to request any study records or records relevant to the research subject eligibility or medical history. Review of study records may include, but are not limited to:
- 4.4.1. Signed consent documents.
- 4.4.2. Source documentation.
- 4.4.3. Logs or checklists.
- 4.4.4. Narrative forms and/or notes-to-file (when applicable).
- 4.4.5. Regulatory and IRB binders or files.
- 4.4.6. Test articles – Drug and device.
- 4.4.7. Medical records that serve as source documents.
- 4.4.8. Any other relevant procedures, materials, or documents.

4.5. The Primary Investigator (PI) is expected to fully cooperate with the audit and make available time for discussion, access documents under review, and personnel on stand-by to answer questions or obtains study records.

4.6. Based upon audit results and feedback from the Primary Investigator, it will be determined that there is:
- 4.6.1. Existence of regulatory non-compliance or lack of subject safety and protection of the research subject.
- 4.6.2. No evidence of non-compliance.
- 4.6.3. Need for implementing quality improvement measures or a CAPA plan.

4.7. The IRB will be notified of evidence of suspected serious non-compliance or continued non-compliance audit findings.

4.7.1. The IRB will make the determination of serious or continuing non-compliance and follow up actions (e.g. follow-up review, notification of Sponsor or regulatory authorities, monitoring of informed consent process, suspension, or termination).

5. Procedures

5.1. Request for For-Cause Audit

5.1.1. The Office of Research Compliance and Quality Improvement will be notified of a for-cause audit request by the IRB, IRB Chairperson, designee, Institutional Official, or regulatory agency (e.g. FDA, NIH, and OHRP).

5.1.2. The request will name the PI, protocol ID number, reason for the audit, and details of the specific information that is required from the audit.

5.1.3. The audit may focus on a specific area of complaint or it may extend into other areas if deemed necessary. The request may include, but may not be limited to:

5.1.3.1. Determine the frequency and nature of any alleged non-compliance.

5.1.3.2. Verify serious non-compliance and/or continuing non-compliance with HRPP policies and applicable federal regulations and laws.

5.1.3.3. Determine if and how subjects were harmed by non-compliance.

5.1.3.4. Determine the root cause(s) of non-compliance.

5.1.3.5. Assess the integrity of the research data.

5.1.3.6. Assess adherence to protocol.

5.1.3.7. Assess accurate record keeping.

5.1.3.8. Assess a protocol involving an investigator unresponsive to IRB requests.

5.1.3.9. Investigate breach of HIPAA.

5.1.3.10. Investigate for unauthorized access by individuals not approved by the IRB.

5.1.3.11. Determine if there have been informed consent violations.

5.1.3.12. Evaluate a study with high volume of subject enrollment.

5.1.3.13. Evaluate an investigator study with significant unanticipated problems or events and serious adverse events.

5.1.3.14. Evaluate an investigator with significant number of protocol violations.

5.1.3.15. Evaluate subject or sponsor complaints.

5.1.3.16. Evaluate concerns from government agencies (e.g. FDA, NIH, and OHRP).

5.1.3.17. Assess for suspected fraud.

5.1.3.18. Review drug/device accountability.
5.1.3.19. Determine if and what type of corrective/remedial actions need to occur.

5.2. Pre-Audit Preparation:

5.2.1. The QI and Education Specialist will conduct the audit within the time frame of the requestor.

5.2.2. The QI and Education Specialist will notify the Principal Investigator and Research Coordinator via email and/or phone:
5.2.2.1. That there is a request for a directed for-cause audit.
5.2.2.2. Reason for the audit.
5.2.2.3. Any IRB determinations (i.e. suspension).
5.2.2.4. Time frame audit will take place.
5.2.2.5. Request for list of all subject IDs.

5.2.3. Additional email notifications will be sent to:
5.2.3.1. Corporate Director of HRPP.
5.2.3.2. McLaren Center for Research and Innovation (MCRI) will be notified if they have oversight over the study.
5.2.3.3. Academic Advisor and Director of Medical Education will be notified if the PI is a resident or student.

5.2.4. Once an appointment date and time has been agreed upon, an official Audit Notification Letter is emailed to the Primary Investigator and Research Coordinator. The letter will contain:
5.2.4.1. The reason(s) for the directed for-cause audit.
5.2.4.2. Date and time of audit.
5.2.4.3. Personnel that should be present.
5.2.4.4. Request for adequate space for the audit.
5.2.4.5. Any hold that the IRB has placed on the research.
5.2.4.6. All documents including complete subject files.
5.2.4.7. Interviews that will be conducted.
5.2.4.8. Planned inspection of the facilities (data storage, drug and device storage, etc.).
5.2.4.9. Whether or not the IRB has requested that the auditor observe the informed consent process with potential participants.
5.2.4.10. Contact number for questions.

5.3. Review of IRB Files

5.3.1. The QI and Education Specialist may study the IRB files in order to become familiar with the protocol and to identify any additional issues that should be focused on during the audit. The following may be reviewed:

5.3.1.1. Initial eProtocol application.
5.3.1.2. Subsequent eProtocol submissions:
5.3.1.2.1. Amendments, revisions, or modifications.
5.3.1.2.2. Continuing reviews.
5.3.1.2.3. Reports.
5.3.1.3. All correspondences to and from IRB including approval letters and notifications.
5.3.1.4. Training records.
5.3.1.5. Clinical Trial Agreements, if applicable.
5.3.1.6. IRB meeting minutes.

5.4. Onsite Audit Activities:

5.4.1. Audit tools and methods may include, but not be limited to:

5.4.1.1. Interview questions.
5.4.1.2. Review of any study records, subject files, source documents, binders, etc.
5.4.1.3. The QI and Education Specialist will audit the selected study using EQuIP compliance worksheets.

5.4.2. Debriefing Interview

5.4.2.1. The QI and Education Specialist will cover the impetus behind the audits and audit process with the PI and research staff.
5.4.2.2. The PI and research staff will have an opportunity to explain or respond to issues that instigated the directed for-cause audit.

5.4.3. Audit of Records

5.4.3.1. The PI does not need to be present during the entire audit. A designated member of the study team must to be available via phone/page or nearby for questions and retrieval of additional material.
5.4.3.2. The documents reviewed will focus on the reason for the audit request and may include, but not limited to:
5.4.3.2.1. Informed consent: forms, process, observation of consenting process.
5.4.3.2.2. Confirmation of subject eligibility.
5.4.3.2.3. Confirmation of protocol procedures and interventions.
5.4.3.2.4. Collecting and reporting adverse events and UPIRSOs.
5.4.3.2.5. Protocol violations or deviations.
5.4.3.2.6. Confidentiality and security measures.
5.4.3.2.7. Subject recruitment, screening, and compensation.
5.4.3.2.8. Subject study and source files.

5.4.3.2.9. IRB, Sponsor, Regulatory Agencies correspondences.
5.4.3.2.10. Monitoring reports.
5.4.3.2.11. Storage facilities for devices, drugs, and biologic.
5.4.3.2.12. Training files.
5.4.3.2.13. Discussion with any individuals involved in study activities.

5.4.3.3. Other documents will be reviewed at the discretion of the QI and Education Specialist.

5.4.3.4. Once the audit is complete, the designated study team member will return study files/records.

5.4.3.5. The length of the audit is dependent on many factors such as the reason for the audit, the type of study, the number of subjects, how long the study has been open, etc.

5.4.3.6. The QI and Education Specialist documentation of findings will be a based on:

5.4.3.6.1. The information contained in the eProtocol application approved by the IRB.
5.4.3.6.2. Review of written study records reflecting study conduct.
5.4.3.6.3. Verbal report from the PI and research personnel.
5.4.3.6.4. Applicable policies, regulations, and ICH GCP guidelines.

5.4.3.7. Audit findings will be documented on the EQuIP compliance worksheets.

5.4.4. Preliminary Findings

5.4.4.1. The QI and Education Specialist will meet with the PI and/or designee to discuss preliminary findings and to allow an opportunity to correct, explain, and/or ask questions.

5.4.4.2. Feedback will be sought regarding the IRB process, educational/training programs, as well as other aspects of the human research protections program at MHC.

5.4.4.3. The QI and Education Specialist will provide recommendations and describe the next set of steps in the process.

5.4.4.4. The exit interview occurs upon completion of the audit but may be deferred if there is a conflict in scheduling (i.e. PI is in surgery).

5.4.4.4.1. A deferred discussion may occur via the phone or email.

5.5. Post Audit Activities

5.5.1. If the findings reveal an immediate threat to subject rights, safety and welfare, the IRB chair and Corporate Director of HRPP will be notified.

5.5.1.1. When appropriate, the policy *MHC_RP111_Study Suspension, Termination and Investigator Hold* will be followed.
5.5.1.2. A follow-up report will be created as in section 5.5.2.

5.5.2. Written Audit Report

5.5.2.1. Upon completion of the audit, the information collected will be analyzed and a Post Audit Summary Report will be generated within 5 business days. The report will address:
5.5.2.1.1. Report on findings specific to the request.
5.5.2.1.2. All other findings where the investigator did not adhere to applicable federal regulations, MHC HRPP policies, ICH GCP guidelines or the protocol.
5.5.2.1.3. Corrective Action Preventative Action Plan, if applicable (see 5.5.3 for CAPA plan procedures).
5.5.2.2. If there are indications of serious or continuing non-compliance the IRB will be notified.
5.5.2.2.1. The IRB will make the determination of serious or continuing non-compliance and follow up actions (e.g. follow-up review, notification of Sponsor or regulatory authorities, monitoring of informed consent process, suspension or termination).

5.5.3. Primary Investigator CAPA Plan Procedures

5.5.3.1. If the PI must complete a CAPA Plan, the PI will have 30 days from submission of the Post Audit Summary Report Letter.
5.5.3.2. In the event the PI requires more than 30 days to develop, document and submit the CAPA plan, or has questions or concerns regarding the process, the PI or coordinator must contact the EQuIP Office.
5.5.3.3. The PI will then have the opportunity to respond in writing to each find in the audit, either challenging the finding or offering additional supporting evidence.
5.5.3.4. If the CAPA Plan is not received by the given deadline, the QI and Education Specialist will send an email reminder to the PI and coordinator.
5.5.3.5. Once the responses to the CAPA plan are received, the Corporate Director of HRPP will review the response.
5.5.3.5.1 If the CAPA Plan is approved the EQuIP Office will email a Closeout Letter.
5.5.3.5.2. The Closeout Letter will include a statement on future follow-up visits, if deemed necessary, to ensure adherence to the CAPA Plan.
5.5.3.5.3. If CAPA Plan is not approved:
5.5.3.5.3.1. The EQuIP Office will return the CAPA Plan with a cover letter.

5.5.3.5.3.2. The cover letter will explain the deficiencies in the response and request a revision.

5.5.3.5.3.3. The PI will have 2 weeks to revise and correct the CAPA plan.

5.5.3.6. The time between receipt of the CAPA Plan and Closeout Letter will depend upon request for additional information or revision of response by the PI.

5.5.4. Dissemination Post Audit Summary Report and Closeout Letter will be sent to:

5.5.4.1. Primary Investigator.

5.5.4.2. Requestor of the Audit.

5.5.4.3. Corporate HRPP Director.

5.5.4.4. Academic Advisor and Director of Medical Education if PI is a resident or student.

5.5.4.5. McLaren Center for Research Innovation (MCRI) management if they have oversight over the involved MHC site.

5.5.5. Verbal Audit Report

5.5.5.1. The QI and Education Specialist may present the audit findings at a convened IRB meeting.

5.5.6. Retention of Audit Documents

5.5.6.1. The PI's electronic audit files will be stored on a password-protected computer in the Office of Research Compliance and Quality Improvement.

5.5.6.2. Paper audit files will be locked in a file cabinet of the Office of Research Compliance and Quality Improvement.

5.5.6.3. The audit documents will be stored for 3 years at the Office of Research Compliance and Quality Improvement.

6. Responsibilities

6.1. Quality Improvement and Education Specialist:

6.1.1. Responsible for conducting directed for cause audits of MHC research studies to ensure compliance with applicable federal regulations and/or agency specific requirements, state or local laws, and institutional policies and procedures.

6.1.2. Generate written reports with results of site review and identify strength and deficiencies or deviations from federal regulations, local laws, institutional policies and Good Clinical Practice.

6.1.3. Responsible for preparing and presenting reports to the Corporate HRPP Director.

6.2. Principal Investigator (PI):

6.2.1. Responsible for the conduct and oversight of their research study, including oversight of personnel and for protecting the right, safety, and welfare of the subjects enrolled in the research.

6.2.2. Responsible for making available study documents for review or audit and addressing concerns or deficiencies via interview and/or CAPA plan.

6.3. IRB:

6.3.1. Responsible for assuring that research studies are approved in accordance with federal, state, and local regulations as well as the HRPP policies and procedures.

6.3.2. Responsible for making available time as well as addressing concerns or deficiencies via interview and/or CAPA plan.

6.4. Corporate Director of HRPP

6.4.1. Responsible for developing, managing, and evaluating policies and procedures that ensure compliance with all state and federal regulations governing research.

6.4.2. Responsible for developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.

6.4.3. Instituting Corrective Action Plans based upon audit findings.

7. References

7.1. 45 CRF 46.113 Suspension or termination of IRB approval of research

7.2. 21 CFR 56.113 Suspension or termination of IRB approval of research

7.3. 45 CFR 46.109(e) IRB Review of Research

7.4. 21 CFR 56.109(f) IRB Review of Research

7.5. 21 CFR 56.108(a) IRB Functions and Operations

7.6. 45 CFR 46.103(b)(4) Assuring compliance with this policy

7.7. OHRP Guidance on Written Procedures, January 2007

7.8. Terms of the Federalwide Assurance, #4 on written procedures

7.9. MHC_RP111_Study Suspension, Termination and Investigator Hold"

7.10. MHC_RP0123_Complaints and Non-Compliance in Human Subject Research

7.11. MHC_RP0124_Reporting to Regulatory Agencies and Institutional Officials

7.12. MHC_RP301_Education and Quality Improvement Program – EQuIP

7.13. EQuIP Compliance Worksheets

8. Appendix

8.1. None

9. Previous Revisions

9.1. None

10. Supersedes Policy

10.1. None

Approvals:

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Michael McKenna, MD Date
Executive Vice President/ Chief Medical Officer
Institutional Official of Research