McLaren HEALTH CARE		Policy Title:	Continuing Review of Human Subject Research
Effective Date:	January 16, 2012	**Policy Number:**	MHC_RP0112
Review Date:	August 11, 2020	**Section:**	Research Integrity
Revised Date:	January 12, 2023	**Oversight Level:**	Corporate
Administrative Responsibility:	Corporate Manager of Research Integrity Institutional Official, HRPP		

1. Purpose

1.1. To define the procedures McLaren Health Care Institutional Review Board (MHC IRB) will follow during continuing review of approved non-exempt human subject research.

1.2. To ensure the McLaren Health Care Institutional Review Board (MHC IRB) and Principal Investigators (PI) meet the responsibilities associated with continuing review for human subjects' research.

2. Scope

2.1. The Human Research Protections Program (HRPP) applies this policy to all proposed activities that meet definitions of "research" and "human subject," the Food and Drug Administration (FDA) definitions of "clinical investigation" and "human subject" and

2.1.1. The research is conducted by or under the direction of an MHC investigator in connection with his/her assignment.

2.1.2. The research is conducted by an investigator employed by MHC or one of its subsidiary hospitals.

2.1.3. The research is conducted using any property, patient population, or facility of MHC or its subsidiary hospitals.

3. Definitions

3.1. Refer to Appendix I *"Definitions"*

4. Policy

4.1. The MHC IRB is responsible for reviewing and approving research which meets the criteria for continuing review as outlined in federal regulations, state and local laws and corporate policies and procedures. This policy is to ensure PIs submit a complete request for continuing review to the MHC IRB at least 30 days prior to the

renewal date when continuing review is required. Requests that are incomplete or lack necessary supporting documentation are not guaranteed to receive approval by the date of expiration.

4.2. When continuing review is no longer required per revised Common Rule, the MHC IRB will determine an Annual Status Report is required.

4.3. With some exceptions (outlined below), continuing review must occur if research remains active. Investigators will be informed when a status report may be submitted in lieu of continuing review via IRB correspondence.

Unless required by the IRB, continuing review is not required for research that is not subject FDA regulations or the pre-2018 version of the Common Rule in the following circumstances:

4.3.1. Research that qualifies for expedited review;

4.3.2. Exempt research that underwent limited IRB review;

4.3.3. Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

4.3.3.1. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

4.3.3.2. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care

4.4. The IRB will determine whether the research continues to satisfy the criteria for approval.

4.5. At the time of continuing review of research protocols, the MHC IRB will make a determination regarding the frequency of review. When continuing review is required, research will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The IRB's determination regarding review frequency will be reflected in the meeting minutes.

4.6. The MHC IRB recognizes that protecting the rights and welfare of subjects sometimes requires the IRB independently verify that no material changes occurred during the IRB-designated approval period, utilizing sources other than the investigator. In some instances, independent verification may be necessary., For example, in cooperative studies or other multi-center research.

4.6.1. The IRB will determine the need for verification from outside sources on a case-by-case basis and according to the following criteria:

4.6.1.1. Protocols where concern has been raised about possible material changes occurring without IRB approval, based on information provided in continuing review reports or from other sources.

4.6.1.2. Protocols conducted by principal investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.

4.6.1.3. Protocols subject to internal audit.

4.6.1.4. Whenever the IRB otherwise deems verification from outside sources to be relevant.

4.6.1.5. The following factors will also be considered when determining which studies require independent verification:

4.6.1.5.1. The probability and magnitude of anticipated risks to subjects.

4.6.1.5.2. The likely medical condition of the proposed subjects.

4.6.1.5.3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.

4.6.2. In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may retrospectively require such verification at the time of continuing review, review of modifications, non-compliance and/or unanticipated problems.

4.6.3. If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken.

4.7. Failure to submit continuing review information on time is non-compliance and will be handled according to the non-compliance policy.

5. Procedure

5.1. Mechanism(s) for Submission:

5.1.1. MHC IRB continuing review applications must be submitted via the IRB electronic application system system. The application must be completed in full with all questions answered in their entirety.

5.2. Submission Processing:

Annual Status Report

5.2.1. Annual Status Report (ASR) will undergo administrative Processing in the IRB electronical system (non-FDA regulated protocol subject to the revised Common Rule approved on or after January 21, 2019).

5.2.2. The PI is sent a reminder 90, 60 and 30 days before ASR due. The PI is responsible for responding to request in time ASR due date noted in the approval letter.

5.2.2.1. Failure to complete this report will be considered non-compliance.

5.2.3. Requirement to submit modifications, changes to personnel, changes to recruitment material, reportable events, and final reports to the IRB have not changed.

5.2.4. Once the project is completed, the PI will submit a final report in the IRB electronic application system.

5.2.5. The IRB Staff will process ASR:

5.2.5.1. Submission will be checked for completeness (e.g., all questions adequately addressed, current consent form attached, training is current for all researchers listed on the research study).

5.2.5.2. Additional questions will be asked by IRB staff as necessary.

5.2.5.3. IRB staff will escalate ASR to IRB chair for review if necessary, including but not limited to:

5.2.5.3.1. History of serious or repeated non-compliance.

5.2.5.3.2. Amendment or report of new findings in study.

5.2.5.4. IRB staff will submit letter to PI.

5.2.5.5. IRB staff will place study on IRB agenda to advise IRB members.

Continuing Review

5.3. PI Submission

5.3.1. To assist investigators, IRB electronic application system will generate a courtesy reminder notice to the PI and the documented contact person. Reports are generated daily for studies due to expire in 90, 60 and 30 days.

5.3.2. However, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

5.3.3. Investigators must submit the following for continuing review:

5.3.3.1. Continuing review application including any proposed modifications.

5.3.3.2. Relevant multi-center trials reports: including the most recent data and safety monitoring report, if not previously submitted and if applicable.

5.3.3.3. When applicable, the current consent document and any newly proposed consent documents.

5.3.3.4. Any other relevant study documentation which will allow the IRB to review the science and ethics of the study and make a determination regarding approval.

5.4. Materials Provided to IRB Members:

5.4.1.1. The primary reviewer or assigned expedited reviewer will access and review the submission materials outlined in 5.4.3, the protocol, and other relevant documents (e.g., approved modifications, interim reports, investigator brochures, etc.) via the IRB electronic system. For studies requiring full board review, all reviewers will have access to the entire application and supporting documentation.

5.4.1.2. IRB members can access any IRB file including protocol modifications previously approved by the IRB.

5.4.1.3. IRB members are provided and review the full protocol, including currently approved protocol if applicable, application, or a protocol summary containing the relevant information necessary to determine whether the proposed research continues to fulfill the criteria for approval.

5.5. Continuing Review Process

5.5.1. In conducting continuing review of research not eligible for expedited review, IRB members are provided with and review all the above-mentioned material. The IRB will review and approve protocols using the criteria at federal regulations 45 CFR 46 and, for FDA research studies, 21 CFR 56, as required. The criteria for IRB approval must be met to approve or recommend approval of the application.

5.5.1.1. The IRB considers the following points in performing continuing review.

5.5.1.1.1. Assessment of actual risks and benefits against anticipated risks and benefits.

5.5.1.1.2. Whether any of the following have occurred:

5.5.1.1.2.1. Harm to subjects.

5.5.1.1.2.2. Problems or accidents.

5.5.1.1.2.3. Unanticipated problems, adverse events, change in the research environment, or new knowledge that the research study poses greater risk to subjects than expected when the study was previously approved and if so, whether shared with subjects.

5.5.1.1.2.4. Significant new findings that might relate to subjects' willingness to continue and, if so, has or will the information be provided to subjects or will subjects re-consent.

5.5.1.1.2.5. Complaints by the subjects or their representatives related to their participation in the study.

5.5.1.1.2.6. Progress reports.

5.5.1.1.3. IRB will consider whether there should be an independent verification (e.g., by EQuIP) that no material changes had occurred without IRB approval since the last review.

5.5.2. When applicable, the consent form will be evaluated to determine if the consent is still accurate and complete, or whether revisions are necessary.

5.5.2.1. The evaluation will be based on the information provided in the application, including new findings, and any changes to the research study, risks, and benefits that might relate to the subject's willingness to continue.

5.5.2.2. If it is determined that it is necessary to include new information, the IRB will consider whether it should be provided to all past subjects as well as new enrollees, or only to new enrollees. If information is expected to be provided to past subjects, the IRB should consider whether an information sheet is sufficient or if a re-consenting process is necessary.

5.5.2.3. If information provided at the time of renewal (e.g., subject complaints, unanticipated problems, evidence of increased risk) indicates that subjects may be at risk, the IRB will give immediate consideration whether to:

5.5.2.3.1. Stop accrual of subjects and/or restrict activities.

5.5.2.3.2. Suspend approval of the protocol.

5.5.2.3.3. Notify officials who will take appropriate action.

5.5.3. Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB. **Informed consent documents should also be reviewed whenever new information becomes available** that would require modification to the content of the informed consent document.

5.5.4. It's the IRB responsibility to protect human subjects during the study. The IRB should examine the progress of study including expected rates screen failures, enrollment.

5.5.5. At any time during the renewal process, the IRB Chair or IRB may determine that it is necessary to suspend protocol in order to protect subjects. If this occurs, policy *MHC_RP111 "Study Suspension, Termination and Investigator Hold"* will be followed.

5.6. Lapses in Continuing Review:

5.6.1. The regulations don't permit a grace period or approval extension after expiration. Research that continues after the approval period has expired is research conducted without IRB approval and is considered non-compliance. If continuing review does not occur by set by the IRB, all research activities must stop after the date of expiration. This includes recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interest of individual subjects to continue participating in the research interventions or interactions. Research activity must cease, even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review prior to the expiration date.

5.6.1.1. Failure to meet continuing review obligations may be grounds for suspension or termination of the research.

5.6.2. The IRB Office is responsible for immediately notifying the investigator of the expiration of approval and that all research activities must stop. This notice will be sent via the Send Email function in the IRB electronic application system.

5.6.3. Upon notification of expiration, the PI must immediately submit to the IRB Chair a list of currently enrolled research subjects for whom suspension of the research would cause harm. Enrollment of new subjects cannot occur and continuation of research interventions or interactions for already enrolled subjects may only continue when the IRB has determined that it is in the best interest of the individual subjects to do so.

5.6.4. OHRP and FDA Guidance – Principal investigator interim decision regarding continuation of certain activities until review by the IRB/Chair can occur:

5.6.4.1. *The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made initially by the investigator, possibly in consultation with the subjects' treating physicians (if the investigator is not the subjects' treating physician), but the investigator as soon as possible should submit a request for confirmation that the IRB agrees with this determination.*

5.6.4.2. *The determination by the IRB may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects.*

5.6.5. Permitting IRB approval to expire without stopping all research-related activities is considered noncompliance, which which will be deemed by the IRB as serious or non-serious, and continuing or non-continuing as per *Policy MHC_RP123 "Complaints and Non-Compliance in Human Subjects Research".*

5.6.6. Once approval has expired, IRB review and re-approval must occur prior to re-initiation of the research.

5.6.6.1. If the study approval has lapsed 14 days or less and the PI provides the required continuing review information, the existing protocol may be reviewed for consideration of continued IRB approval.

5.6.6.2. If the study approval has lapsed more than 14 days and the PI has not provided the required continuing review information, the PI must submit a new application to the IRB for review and approval.

5.6.6.3. If the IRB approves the protocol, the new approval date will reflect the date when the study was re-approved by the IRB.

5.6.7. If a research protocol receives contingent approval at the time of the continuing review, and the previous approval expires before the PI responds to the contingencies, no new subjects may be enrolled, and no medical records may be accessed after the approval expiration date except to ensure subject safety.

5.6.7.1. Upon receipt of response from the PI, the existing protocol will be reviewed for continuation.

5.6.7.2. If the PI does not respond within 30-days, the IRB may vote to administratively close the study. Decisions of this kind will be made in a manner

that ensures that closure will not harm any enrolled participants who may require ongoing treatment as part of the research study.

5.7. Expedited Review

5.7.1. The IRB chair or an assigned reviewer will serve as the primary reviewer for expedited submissions and has the authority to approve or require modifications to the submission. The primary reviewer does not have the authority to disapprove expedited submissions. If the reviewer feels that a submission is not fit for approval, it must be referred to the fully convened IRB for consideration.

5.7.2. The reviewer will be provided with all the material submitted by the PI to conduct their review. The reviewer is provided access to the same materials as would occur for full board review.

5.7.3. Per Research Integrity policy *MHC_RP106 "Expedited Review of Human Subject Research*", the reviewer will determine whether the research continues to meet the federal criteria for approval, by completing the *Review Checklist: Continuing Review.*

5.7.4. Research studies which have been initially approved by expedited review can be renewed by expedited procedures, unless changes in the protocol have been made such that the research no longer qualifies for expedited review.

5.7.5. Research studies initially approved by the fully convened IRB undergo review by the fully convened IRB; however, expedited review procedures may be used under:

5.7.5.1. Category 8: (a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; *and* (iii) the research remains active only for long-term follow-up of subjects; or

5.7.5.1.1. (b) where no subjects have been enrolled and no additional risks have been identified; or

5.7.5.1.2. (c) where the remaining research activities are limited to data analysis.

5.7.5.2. Category 9: Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

6. Responsibilities

6.1. Principle Investigator: Must provide the IRB with all relevant information regarding the conduct of the research and are expected to:

6.1.1. Complete and submit the continuing/final review application and all applicable addendums prior to the annual renewal date and in time for review.

6.1.2. Ensure PI, co-investigator(s) and all key personnel have current human subject protection education certification.

6.1.3. Provide all applicable documents as outlined in this policy.

6.1.4. Provide any additional information or clarification requested by the fully convened IRB, IRB Chair, or designee, in a timely fashion in order to assist in the determination of approval.

6.1.5. Failure to respond may result in expiration of the IRB approval.

6.2. IRB Staff:

6.2.1. Advise PI and research staff in preparation and completion of the application process.

6.2.2. Conduct a pre-review of the application and supporting documents for completeness and to identify non-scientific issues.

6.2.3. Ensure all applicable documents have been provided.

6.2.4. Submit concerns to the study team for incomplete submissions, clarifications, or minor changes to allow for scientific and ethical review by the fully convened IRB or designee.

6.2.5. Confirm study type (e.g., expedited, or full board review) is appropriate as submitted by the PI and request changes in accordance with federal regulations, state and local laws, and institutional policies and procedures.

6.2.6. When applicable, schedule full board continuing review applications to the next available convened IRB meeting.

6.2.7. Assign full board continuing review applications to a primary reviewer(s) and secondary reviewer(s) (if necessary).

6.2.8. Ensure IRB has adequate representation during the evaluation of the proposed human subject's research.

6.2.9. Assign expedited applications to the IRB chair or qualified reviewer for review.

6.2.10. Ensure IRB members with COI are not present during the review and approval of the study.

6.2.11. Prepare IRB correspondence to the investigator.

6.3. IRB:

6.3.1. Review all material provided with the submission for review and determination of whether the proposed human subjects research meets the federal criteria for approval.

6.3.2. Ensure additional safeguards have been included to protect the rights and welfare of vulnerable populations when some or all the subjects are likely to be vulnerable to coercion or undue influence, such as prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

6.3.3. Request a motion from the primary IRB reviewer for each submission, if applicable.

6.3.4. Reviewers will make recommendations to the fully convened IRB. These recommendations can be accepted as presented, modified, or rejected by a motion and passed by a majority.

6.3.4.1. Have the authority to vote on the final determinations of those recommendations.

7. References:

7.1. 21 CFR 50

7.2. 21 CFR 56

7.3. 45 CFR 46

7.4. HRPP MHC_RP0106 “Expedited Review of Human Subject Research”

7.5. HRPP MHC_RP0111 “Study Suspension, Termination and Investigator Hold”

7.6. HRPP MHC_RP0123 “Non-Compliance in Human Subjects Research”

7.7. Appendix I “Definitions”

8. Previous Revisions: 12/3/12, 3/18/13, 8/11/20, 12/14/21

9. Supersedes Policy: MHC_RP0113 Continuing Review of Human Subject Research

10. Approvals:

MHC Institutional Review Board initial review: 2/17/12

MHC Institutional Review Board acknowledgment:12/21/12, 12/4/15

Signature on File *1/31/23*

Justin Klamerus, MD, MMM Date
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