McLaren HEALTH CARE		Policy Title:	Continuing Review of Human Subject Research
Effective Date:	January 16, 2012	Policy Number:	MHC_RP0112
Review Date:	December 4, 2015	Section:	Human Research Protections Program (HRPP)
Revised Date:	November 16, 2015	Oversight Level:	Corporate
Administrative Responsibility:	Corporate Director, HRPP Institutional Official, HRPP		

1. Purpose

1.1. The purpose of this policy is:

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

1.1.2. 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 a MHC investigator in connection with his/her assignment.

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

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

2.2. Continuing review applies to all remaining activities which include data collection, analysis of identifiable private information, or the research remains active for long-term follow-up of subjects, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions.

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 the 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 annual renewal date. Requests that are incomplete or lack necessary supporting documentation are not guaranteed to receive approval by the date of expiration.

4.2. Continuing review must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research-related interventions. Continuing review of research must occur even when the remaining research activities are limited to the analysis of private identifiable information.

4.3. At the time of continuing review, the MHC IRB will make a determination regarding the current level of risk associated with the research. Risks associated with the research will be classified as either "minimal" or "greater than minimal". The meeting minutes will reflect the Committee's determination regarding risk levels.

4.4. The IRB will determine whether study continuation is consistent with ensuring the participant's continued welfare.

4.5. At the time of continuing review, the MHC IRB will make a determination regarding the frequency of review of the research protocols. All protocols 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 meeting minutes will reflect the IRB's determination regarding review frequency.

4.6. The MHC IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occurred during the IRB-designated approval period. Independent verification from sources other than the investigator may be necessary at times, 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 about possible material changes occurring without IRB approval have been raised 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 else the IRB deems verification from outside sources is 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 amendments 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 e-protocol online system. The application must be completed in full; all questions must be completed.

5.2. Submission Processing:

5.2.1. The IRB Staff checks for completeness (e.g., all questions completed, current consent form attached). IRB Staff verifies current training for all researchers listed on the research study.

5.2.2. IRB Staff will notify the PI of any individuals without current training and those individuals must have current training before the renewal approval letter can be issued.

5.3. Materials Provided to IRB Members:

5.3.1. The assigned reviewer will access the continuing review application, current consent form (if applicable), and any supporting documents via the e-protocol online system. All reviewers will have access to the entire application and all the supporting documents.

5.3.2. All Members can request access to any IRB file including any protocol modifications previously approved by the IRB.

5.4. Continuing Review Process:

5.4.1. To assist investigators the MHC IRB Office staff (via e-protocol online system) will send out renewal notices to investigators 90-60-30 day in advance of the expiration date; 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.

5.4.2. Investigators must submit the following for continuing review:

5.4.2.1. The continuing review application updated with any changes;

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

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

5.4.2.4. 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.

5.4.3. In conducting continuing review of research not eligible for expedited review, IRB reviewers are provided with and review all of the above material. The IRB member(s) are required to review and approve protocols using the criteria at federal regulations 45 CFR 46 and, for FDA research studies, 21 CFR 56. The criteria for IRB approval must be met to approve or recommend approval of the application.

5.4.3.1. The IRB considers the following points in performing continuing review:

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

5.4.3.1.2. Whether there have been any:

5.4.3.1.2.1. Harm to subjects.

5.4.3.1.2.2. Problems or accidents.

5.4.3.1.2.3. 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.

5.4.3.1.2.4. 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.

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

5.4.3.1.2.6. Progress reports.

5.4.3.1.2.7. When applicable, accuracy of consent form and need for revision.

5.4.4. When applicable, the consent form will be evaluated to determine if the consent is still accurate and complete.

5.4.4.1. Based on the continuing review application, the consent form will be evaluated to determine if findings that might relate to the subject's willingness to continue should be included in the consent form. The evaluation will be based on the information provided in the application, including information on new findings, any changes to the research study, risks, and benefits.

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

5.4.4.3. 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, an immediate issue to consider will be whether to:

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

5.4.4.3.2. Suspend approval of the protocol.

5.4.4.3.3. Notify officials who will take appropriate action.

5.4.5. Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

5.4.6. At any time during the renewal process the IRB Chair or IRB may determine that it is necessary to act to protect subjects by suspending the protocol. If this occurs, the Policy *MHC_RP111 "Study Suspension, Termination and Investigator Hold"* will be followed.

5.5. Expedited Review of Continuing Review:

5.5.1. In conducting continuing review under expedited review, the reviewers receive all of previously noted material. The reviewer(s) complete the "*Review Checklist: Continuing Review*" to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval.

5.5.2. Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367 (refer to Policy *MHC_RP106 "Expedited Review of Human Subject Research*"). It is also possible that research activities that previously qualified for expedited review in accordance with 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

5.6. Lapses In Continuing Review:

5.6.1. The regulations permit no grace period or approval extension after approval expiration. Research that continues after the approval period has expired is research conducted without IRB approval and is considered as non-compliance. If the continuing review does not occur within the timeframe set by the IRB, all research activities must stop, including recruitment (media advertisements must be pulled), enrollment, consent, interventions, interactions, and data collection, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions.. This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must allow sufficient time for IRB review before the expiration date.

5.6.1.1. The 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 is send via eProtocol electronic submission system.

5.6.3. If research participants are currently enrolled in the research project and their participation is ongoing, once notified of the expiration of approval the PI must immediately submit to the IRB Chair a list of 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 should only continue when the IRB or IRB Chair finds that it is in the best interest of the individual subjects to do so.

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

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

5.6.5.1. 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.

5.6.5.2. 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.

5.6.5.3. If the IRB approves the protocol, the new approval date will be that of the date will reflect the date when the study was re-approved by the IRB.

5.6.6. 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, the PI may not enroll any new subjects or access medical records after the approval expiration date.

5.6.6.1. Once the PI responds, the existing protocol will be reviewed for continuation.

5.6.6.2. If the PI does not respond within 30-days, the IRB may vote to administratively close the study. Decisions of this kind must be made in a manner that ensures that closure will not harm any participants previously enrolled who may require ongoing treatment as part of the research study.

5.7. Expedited Review

5.7.1. IRB Chair or assigned reviewer serves as the primary reviewer for expedited submissions and has the authority to approve, or require modifications to expedited submissions. The Chair or assigned reviewer does not have the authority to disapprove expedited proposals but must refer these for consideration by the fully convened IRB.

5.7.2. Reviewer is provided with all the material submitted by the PI in order to conduct their review;

5.7.3. Determines whether the proposed human subjects research meet the federal criteria's for approval, per HRPP Policy *MHC_RP106 "Expedited Review of Human Subject Research*". The IRB Chair or assigned reviewer completes the reviewer checklist for applications meeting the criteria for expedited 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 that affect subject safety, rights, welfare, or risk;

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 the following conditions. Continuing review of research previously approved by the convened IRB as follows:

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. PIs: Are to provide the IRB with all relevant information regarding the conduct of the research.

6.1.1. PIs are expected to:

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

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

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

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

6.1.1.5. Failure to respond might result in expiration of the IRB approval.

6.2. IRB Staff:

6.2.1. e-Protocol will generate a courtesy reminder notice to the PI and the documented contact person. Reports are generated on a daily basis and reflect studies due to expire in 90, 60 and 30 days;

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

6.2.3. Conduct a pre-review of the application and supporting documents to identify non-scientific issues;

6.2.4. Ensure all applicable documents have been provided;

6.2.5. 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 the IRB Chair or their designee;

6.2.6. 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;

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

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

6.2.9. Ensure IRB has adequate representation during the evaluation of the proposed human subjects research;

6.2.10. Assign expedited applications to the IRB Chair or qualified reviewer for review;

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

6.2.12. Prepare IRB correspondence to the investigator using e-Protocol.

6.3. IRB:

6.3.1. Will review all material submitted by the PI for review. Staff determines whether the proposed human subjects research meet the federal criteria's for approval.

6.3.2. When some or all of 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, the IRB will ensure additional safeguards have been included in the study to protect the rights and welfare of these subjects.

6.3.3. Request the motion, for each submission, by the IRB primary reviewer, if applicable;

6.3.4. Have the authority and should 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: December 3, 2012, March 18, 2013

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

10. Approval:

MHC Institutional Review Board initial review:	February 17, 2012
MHC Institutional Review Board acknowledgment:	December 21, 2012 December 4, 2015

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Michael McKenna, MD. Date

Executive Vice President/Chief Medical Officer

Institutional Official of Research