McLaren HEALTH CARE		**Policy Title:**	Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)
Effective Date:	January 16, 2012	**Policy Number:**	MHC_RP0121
Review Date:	April 14, 2016	**Section:**	Human Research Protections Program (HRPP)
Revised Date:	March 30, 2016	**Oversight Level:**	Corporate
Administrative Responsibility:	Corporate Director, HRPP Institutional Official, HRPP		

1. Purpose

1.1. To ensure the protection of the rights, safety, and welfare of human subjects and to provide the guidelines for investigators for recognizing and promptly reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO) to MHC IRB.

1.2. This policy also establishes guidelines for the IRB in reviewing reported events and reporting appropriately.

2. Scope

2.1. This policy applies to all individuals conducting human subject research under the auspices of McLaren Health Care Corporation and its subsidiary hospitals;

2.2. This policy and procedures reflects the U.S. Office for Human Research Protection's (OHRP) current guidance on unanticipated problems involving risk to subjects or others and adverse events.

2.2.1. Only a small subset of adverse events occurring in human subjects participating in research will meet the definition of an unanticipated problem involving risk to subjects or others.

3. Definitions

3.1. Protocol Violations are those that:

3.1.1.1. Affect the rights, safety, or welfare of study subjects;
3.1.1.2. Change the risk/benefit ratio;
3.1.1.3. Affect the scientific design of the study, OR;
3.1.1.4. Violate an ethical principle

3.2. **Unanticipated adverse device effect**: Any serious adverse effect on health or safety; or any life-threatening problem or death caused by, or associated with, a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.150(a)).

3.3. Refer to Appendix I "Definitions" for additional information

4. Policy

4.1. MHC IRB complies with DHHS and FDA regulations which state that institutions must have written policies on reporting unanticipated problems involving risks to subjects or others to the IRB, institutional officials and relevant federal agencies and departments.

4.2. The following procedures describe how unanticipated problems involving risk to subjects or others are handled in research under the auspices of MHC IRB.

5. Procedure

5.1. Reporting

5.1.1. Investigators must promptly report the following problems to the IRB:

5.1.1.1. Adverse events involving direct harm to participants (either local or external) which in the opinion of the principal investigator meet the criteria for an unanticipated problem involving risk to subjects or others.

5.1.1.2. Unanticipated problem involving risks to participants or others refer to any incident, experience, outcome, or new information that:

5.1.1.2.1. Is unexpected: The event is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

5.1.1.2.2. Is related or possibly related to participation in the research: There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; **and**,

5.1.1.2.3. Is serious: The event suggests that the research places subjects or others at a greater risk of harm (including physical,

psychological, economic, or social harm) than was previously known or recognized.

5.1.1.3. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.

5.1.1.4. New information that indicates a change to the risks or potential benefits of the research. For example:

5.1.1.4.1. An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.

5.1.1.4.2. A paper is published from another study that shows that the risks or potential benefits of your research may be different than initially presented to the IRB.

5.1.1.5. A breach of confidentiality.

5.1.1.6. Local Death - regardless of relationship to study treatment or procedure or device implant, during the duration of study treatment and for up to 30 days after the last dose of study treatment or procedure or device implant.

5.1.1.7. Incarceration of a participant in a protocol not approved to enroll prisoners.

5.1.1.8. Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.

5.1.1.9. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.

5.1.1.10. Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.

5.1.1.11. Protocol violation is sponsor-imposed suspension for risk.

5.1.1.12. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

5.1.1.13. Unanticipated adverse device effect

5.1.1.14. Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

5.2. Submission of Reports

5.2.1. Investigators must report possible unanticipated problems to the IRB promptly.

5.2.1.1. If the event requires immediate intervention to prevent serious harm to participants or others, the investigator must report the event within five (5) business days of receiving notice of the event.

5.2.1.2. Investigators must report all other reportable unanticipated problems occurring at the local research site and non-local research sites to the IRB as soon as possible but no later than ten (10) business days from the date the investigator is notified of the event.

5.2.2. Problems occurring within thirty (30) days after participants' active participation or treatment must be reported according to the above schedule.

5.2.3. Investigators or the study team must report possible unanticipated problems to the MHC IRB Office in writing using the Unanticipated Problem Report Form through the electronic submission system. The written report should contain the following:

5.2.3.1. Detailed information about the possible unanticipated problems, including relevant dates.

5.2.3.2. Any corrective action, planned or already taken, to ensure that the possible unanticipated problem(s) is (are) corrected and will not occur again.

5.2.3.3. An assessment of whether any subjects or others were placed at risk as a result of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.

5.2.3.4. When available, if a report from a sponsor is the basis for the report of a possible unanticipated problem involving risks to subjects or others, or a sponsor has requested the submission to the IRB, the report should be accompanied by an analysis from the sponsor detailing (1) how the event or problem satisfies the definition of a UPIRSO, (2) proposed study-wide corrective actions or modifications to the research along with a timeline for anticipated completion of the actions, and (3) whether or not the problem has been reported as a UPIRSO to any relevant federal agencies.

5.2.3.5. Any other relevant information.

5.2.3.6. Any other information requested by the HRPP Office.

5.2.4. A report of a possible unanticipated problem involving risks to participants or others will be immediately forwarded by MHC IRB Office staff to the IRB Chair if the MHC IRB Office staff believes that immediate intervention may be required to protect participants or others from serious harm.

5.2.5. Upon receipt of a report of a possible unanticipated problem from someone other than the investigator or study staff, the IRB Staff will notify the PI on the study when appropriate.

5.3. IRB Procedures for Handling Reports of Possible Unanticipated Problems

5.3.1. Review by IRB Staff and Chair

5.3.1.1. Upon receipt of an Unanticipated Problem Report Form the MHC IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will contact the investigator or the designated contact person to obtain additional information.

5.3.1.1.1. IRB staff may withdraw the form from further review when appropriate.

5.3.1.2. IRB Chair and/or other designated experienced IRB member(s) receives and reviews the report of the event(s) considered to be an unanticipated problem.

5.3.1.2.1. The IRB Chair or designee will make the determination as to whether the event meets the definition of UPIRSO by using the *(Unanticipated Problem Involving Risks to Subjects or Others) Reviewer Checklist* and recommend the following actions:

5.3.1.2.1.1. No action required as event doesn't meet the definition of UPIRSO.

5.3.1.2.1.2. Take immediate action.

5.3.1.2.1.3. Refer to convened IRB for review as likely UPIRSO.

5.3.1.3. Based on the information received from the investigator, the IRB Chair or designee may suspend research to ensure protection of the rights and welfare of participants. Suspension directives made by the IRB Chair or designee must be reported to a meeting of the convened IRB.

5.3.1.4. The IRB, the IRB Chair or designee has authority to require submission of more detailed contextual information by the PI, the sponsor, the study coordinating center, or DSMB/DMC about any adverse event occurring in a research protocol as a condition of the continuation of the IRB's approval of the research.

5.3.1.5. If the IRB Chair or designed reviewer considers that the problem meets the definition of UPIRSO is an unanticipated problem, the reviewer will notify the IRB Staff and review:

5.3.1.5.1. The currently approved protocol.

5.3.1.5.2. The currently approved consent document.

5.3.1.5.3. Previous reports of unanticipated problems involving risks to participants or others.

5.3.1.5.4. The investigator's brochure, if one exists.

5.3.1.6. The IRB Staff will add the event to the agenda for the next MHC IRB convened meeting.

5.3.1.7. All events determined to be unanticipated problems will be reported to the relevant regulatory agencies and institutional officials.

5.3.2. IRB Review by Convened Board

5.3.2.1. The IRB will be provided with the protocol file, the currently approved consent document (if applicable), previous reports of unanticipated problems involving risks to participants or others, the investigator's brochure (if one exists), the event report, and recommendations from the IRB Chair or designee, when appropriate.

5.3.2.2. After review of the protocol and the report form, the full IRB will make findings and recommendations based on the following considerations:

5.3.2.2.1. Whether the reported event is an unanticipated problem involving risks to participants or others according to the definition in this policy.

5.3.2.2.2. What action in response to the report is appropriate.

5.3.2.2.3. Whether suspension or termination of approval is warranted.

5.3.2.2.4. Whether further reporting to Institutional and/or federal officials is required.

5.3.2.3. If the IRB finds that the event is not an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

5.3.2.3.1. No action.

5.3.2.3.2. Requiring modifications to the protocol.

5.3.2.3.3. Revising the continuing review timetable.

5.3.2.3.4. Modifying the consent process.

5.3.2.3.5. Modifying the consent document.

5.3.2.3.6. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation).

5.3.2.3.7. Providing additional information to past participants.

5.3.2.3.8. Requiring additional training of the investigator and/or study staff.

5.3.2.3.9. Other actions appropriate for the local context.

5.3.2.4. If the IRB finds that the event is an unanticipated problem involving risks to participants or others, according to the definition in the policy, the IRB may recommend any of the following actions:

5.3.2.4.1. Requiring modifications to the protocol.

5.3.2.4.2. Revising the continuing review timetable.

5.3.2.4.3. Modifying the consent process.

5.3.2.4.4. Modifying the consent document.

5.3.2.4.5. Providing additional information to current participants (e.g. whenever the information may relate to the participant's willingness to continue participation).

5.3.2.4.6. Providing additional information to past participants.

5.3.2.4.7. Requiring additional training of the investigator and/or study staff.

5.3.2.4.8. Reconsidering approval.

5.3.2.4.9. Requirement that current participants re-consent to participation.

5.3.2.4.10. Monitoring of the research.

5.3.2.4.11. Monitoring of the consent process.

5.3.2.4.12. Referral to other organizational entities (e.g., legal counsel, risk management, institutional official).

5.3.2.4.13. Suspending the research.

5.3.2.4.14. Terminating the research.

5.3.2.4.15. Other actions appropriate for the local context.

5.3.2.5. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research.

5.3.2.5.1. Any suspension or termination of research by the IRB must be promptly reported to the Institutional Official, OHRP, and FDA (if FDA-regulated research). This should be done in writing.

5.3.2.6. If, after reviewing a report, the IRB finds that the event is an unanticipated problem involving risks to participants or others or that suspension or termination of approval is warranted, the IRB will:

5.3.2.6.1. Notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, other affected units and the investigator's supervisor, and

5.3.2.6.2. Report its findings and recommendations to the Institutional Official for further reporting to the appropriate federal officials (OHRP and FDA).

6. Responsibilities

6.1. Investigators:

6.1.1. Be knowledgeable about the MHC IRB reporting requirements and when the event constitutes the UPIRSO.

6.1.2. Must report a UPIRSO promptly, but in all cases within the time frame specified in this document.

6.2. IRB Staff and Administrators:

6.2.1. Review materials submitted to the IRB through the electronic submission system;

6.2.2. Promptly notify the Chair or designee of events that represent eminent risk to participants or other events as appropriate.

6.2.3. Process submissions appropriately.

6.2.4. Record IRB determinations and maintain documentation in accordance with 45 CFR 46 and 21 CFR 56.

6.2.5. Prepare written reports as required by federal regulations, state and local laws, and institutional policies and distribute within applicable timeframes through the eProtocol submission system.

6.2.6. Provide the Institutional Official (IO) and other relevant individuals with updated information as the IRB processes any items governed by this policy.

6.2.7. Review events that do not qualify as UPIRSO and notify the PI of the decision.

6.2.8. Place the UPIRSO reports on the next convened IRB meeting agenda for discussion.

6.3. IRB Chair or designees:

6.3.1. The Chair will review materials submitted and seek consultation with IRB administration as appropriate to make a determination of the action that should be taken.

6.3.2. If the Chair feels that the event meets the definition of UPIRSO, he/she will refer the UPIRSO to the next fully convened meeting for review and determination.

6.3.3. Any incident, experience, or outcome that meets the definition of UPIRSO at a greater risk of harm than was previously known or recognized will be reported to the fully convened IRB.

6.3.4. The Chair has the authority, to suspend enrollment or research procedures to protect participants' safety and welfare immediately upon notification of a UPIRSO. Suspension of enrollment or research procedures will be conveyed immediately to the Principal Investigator and the Chair's or designee's actions will be reported at the next fully convened meeting.

6.4. Convened Institutional Review Board (IRB):

6.4.1. The IRB will review UPIRSOs.

6.4.2. All IRB members will receive a copy of the Report form, the IRB application, protocol and consent document as appropriate. IRB members are expected to review this material. The primary reviewer will also be provided with the most recently approved Investigator's Brochure as appropriate.

6.4.3. The fully convened IRB can take the following actions:

6.4.3.1. No action required.

6.4.3.2. Suspend the study.

6.4.3.3. Terminate the study.

6.4.3.4. Request additional information or follow-up information.

6.4.3.5. Request that the protocol, informed consent, investigator's brochure, and other study related documents be modified to include information regarding the UPIRSO.

6.4.3.6. Modification to the continuing review schedule as appropriate.

6.4.3.7. Request information be provided to subjects who participated in / are be asked to sign a revised informed consent document as deemed appropriate by the IRB.

6.4.3.8. Request information be provided to subjects who previously participated in the research study as necessary.

6.4.3.9. Refer to other organizational entities or committees if applicable.

6.4.3.10. Review actions taken by the Chair or designee regarding suspension of research activities and determine if actions should be continued or lifted.

6.4.3.11. Review an administrative hold placed on a study by a sponsor, a Data Safety and Monitoring Board, a facility at which at the research is conducted, or by another IRB and take appropriate actions to protect the welfare and safety of participants.

6.4.3.12. Determine that a UPIRSO meets the criteria as outlined by OHRP and/or the FDA and therefore requires reporting to regulatory authorities.

7. References

7.1. OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (January 15, 2007)

7.2. FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs Improving Human Subject Protection (January 2009)

7.3. Appendix I "Definitions"

7.4. UPIRSO (Unanticipated Problem Involving Risks to Subjects or Others) Reviewer Checklist

8. Previous Revisions: December 03, 2012, November 18, 2013, November 24, 2015

9. **Supersedes Policy:** MHC_RP0118 Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

10. Approvals:

MHC Institutional Review Board initial approval:	February 17, 2012
MHC Institutional Review Board acknowledgements:	November 19, 2013 December 4, 2015 April 14, 2016

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Michael McKenna, MD Date
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