McLaren HEALTH CARE		Policy Title:	Reportable Events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)
Effective Date:	January 16, 2012	**Policy Number:**	MHC_RP0121
Review Date:	August 17, 2020	**Section:**	Research Integrity
Revised Date:	January 14, 2023	**Oversight Level:**	Corporate
Administrative Responsibility:	Corporate Manager of Research Integrity 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 for reviewing reported events and appropriately reporting to relevant individuals, departments, and agencies.

2. Scope

2.1. This IRB Policy applies to all research conducted at McLaren Health Care and its subsidiaries.

3. Definitions

3.1. Refer to Appendix I *"Definitions"*

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. 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.

4.3. The PI bears responsibility for identifying local unanticipated problems and assuring provision of associated clinical care to safeguard the participants' well-being and rights. The PI also bears responsibility for reporting UPs unanticipated problems (both local and external) to the sponsor and the IRB of record, in accordance with the IRBs policies and for proposing any changes required to ensure protection of human participants.

4.4. The IRB of record may be McLaren IRB or an approved external IRB. The IRB of record is responsible for conducting a meaningful review of the PI's report and deciding whether the event meets criteria as an unanticipated problem, if actions by the PI are adequate and/or if imposing further actions to protect human participants, if necessary. (see MHC_RP0128 Relying on External IRB)

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

5. Procedure

5.1. *Assessment of Potential Unanticipated Problem and Reporting*

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

5.1.1.1. Principal Investigators are responsible for reporting *adverse events* involving direct harm to participants (either local or external) which, in their opinion, that meet the definition of UPIRSOs. These include adverse events that meet the criteria for an *unanticipated* problem involving risk to subjects or others which are unexpected, related, and serious. They may include subject complaints, protocol deviations, and other untoward events involving risk. The IRB Chair or convened IRBs are responsible for making the final determination that a reported event is a UPIRSO.

5.1.1.1.1. 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.

5.1.1.1.2. 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,

5.1.1.1.3. 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.

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

5.1.1.3. New information that is related to the research and indicates that subjects or others might be at increased risk or that the potential benefits of the research are less (e.g., less likely, less significant) than was previously understood. For example:

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

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

5.1.1.4. A breach of confidentiality.

5.1.1.5. Audit findings, inquiry, or written report by a Federal agency (e.g., FDA Form 483).

5.1.1.6. Change in vulnerable populations (e.g., enrollment or inclusion of vulnerable populations without prior IRB approval, or when an existing subject becomes a member of a vulnerable population when the study does not have prior IRB approval for inclusion of the vulnerable population such as the incarceration of a participant in a protocol not approved for the enrollment of prisoners).

5.1.1.7. Local deaths

5.1.1.7.1. Deaths that meet the definition of UPIRSO, regardless of when they occur, must be promptly reported to the IRB.

5.1.1.7.2. Deaths that occur during the study treatment or procedure phase or within 30 days post treatment, regardless of whether the death meets the definition of UPIRSO, must be promptly reported to the IRB.

5.1.1.7.3. The following deaths can be reported at the time of continuing review:

5.1.1.7.3.1. Death due to natural disease progression and other reasons clearly unrelated to the research (e.g., an accident) that occur during the follow up phase of a study (*and more than 30 days after the last day/dose of investigational study treatment or procedure*).

5.1.1.7.3.2. Death that occurs during data collection studies, e.g., surveys, registries.

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

5.1.1.9. Change to the protocol initiated 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 for which there is a 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 effects that are serious, unanticipated, and related (related events may be, probably, or possibly related).

5.1.1.14. FDA believes that only the following AEs should be considered as unanticipated problems that must be reported to the IRB:

5.1.1.14.1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

5.1.1.14.2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

5.1.1.14.3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem.

5.1.1.14.4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations.

5.1.1.14.5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison).

5.1.1.14.6. Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

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

5.1.2. Events That Do Not Require Prompt Reporting

Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") should be described in the informed consent process/form and do not require prompt reporting to the IRB by PIs. The following are examples of events that do not require prompt reporting:

5.1.2.1. Local adverse event or problem that is expected or is not associated with a greater risk of harm to participant or others than previously know. Adverse device effects that are non-serious, anticipated, or unrelated.

5.1.2.2. DSMB reports; interim analyses; or other reports, findings, or new information not altering the risk/benefit profile.

5.1.2.3. Protocol deviations are reported at the time of continuing review **except** if any of the following are true:

5.1.2.3.1. The deviation indicates an increased risk for subjects or compromises their rights or welfare;

5.1.2.3.2. The deviations compromise the scientific integrity of the study or the soundness of the research plan; or

5.1.2.3.3. The deviations represent serious or ongoing non-compliance.

5.1.2.4. Subject complaints that were resolved or complaints not involving risks.

5.1.2.5. External adverse event or problem lacking an analysis documenting that it is unanticipated, related or possibly related and associated with a greater risk of harm than previously known, such as Individual IND Safety or FDA MedWatch reports from external sites without an analysis.

5.1.2.6. Problems or findings not involving risk (unless the PI believes the information could affect subjects' willingness to continue in the research).

5.2. *Submission of Report*

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 seven (7) 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, except for UPIRSO which should be reported at all times.

5.2.3. The investigators or study team must report possible unanticipated problems to the MHC IRB office via the Unanticipated Problem Report Form in the IRB electronic 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 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 because of the event or suffered any physical, social, or psychological harm and any plan to address these consequences.

5.2.3.4. 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 (if available) 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 information relevant to the event.

5.2.3.6. Any other information requested by the HRPP Office.

5.2.4. The MHC IRB office staff will immediately forward reports of possible unanticipated problem involving risks to participants or others to the IRB Chair if it is believed 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 of 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 will check the form for completeness. If any applicable sections of the form are incomplete or have not been answered satisfactorily, the IRB staff will submit comments detailing necessary revisions and/or clarifications via the IRB electron application system to obtain additional information.

5.3.1.2. IRB staff may withdraw the form from further review when appropriate if IRB chair or designee makes initial determination that event does not meet determination of UPIRSO.

5.3.1.3. IRB staff will notify PI in IRB electronic system.

5.3.1.4. IRB staff will promptly notify the IRB chair or designee of events that represent eminent risk to participants or other events, as appropriate.

5.3.1.5. IRB chair and/or other designated experienced IRB member(s) will receive and review the report of the event(s) considered to be an unanticipated problem.

5.3.1.6. The IRB chair or designee will make the initial 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 one of the following actions:

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

5.3.1.6.2. The IRB, the IRB chair or designated IRB member has the 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.

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

5.3.1.6.4. Take immediate action

5.3.1.6.4.1. 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 the convened IRB.

IRB chair or designated reviewer considers that the problem meets the definition of a UPIRSO

5.3.1.7. If the IRB chair or designated reviewer considers that the problem meets the definition of a UPIRSO, the reviewer will notify the IRB Staff and review:

5.3.1.7.1. The currently approved protocol.

5.3.1.7.2. The currently approved consent document.

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

5.3.1.7.4. The investigator's brochure if one exists.

5.3.1.8. The IRB staff will add the event to the agenda for the next convened meeting of the MHC IRB.

5.3.2. *IRB Review by Convened Board*

5.3.2.1. All IRB members will receive a copy of the UPIRSO report form, and all supporting documentation as submitted, 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 applicable), the event report, and recommendations from the IRB chair or the 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. The appropriate action in response to the report.

5.3.2.2.3. Whether suspension or termination of approval is warranted.

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

5.3.2.2.5. Review any administrative hold placed on a study by a sponsor, a data safety and monitoring board, another facility at which at the research is conducted, or by another IRB and take appropriate actions to protect the welfare and safety of participants.

*IRB finds that the event **is not** an unanticipated problem involving risks to participants or others*

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. Require modifications to the protocol.

5.3.2.3.3. Revision of the continuing review timetable.

5.3.2.3.4. Modification of the consent process.

5.3.2.3.5. Modification of the consent document.

5.3.2.3.6. Provision of 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. Provision of additional information to past participants.

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

5.3.2.3.9. Other actions appropriate for the local context.

*IRB finds that the event **is** an unanticipated problem involving risks to participants or others*

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. Require modifications to the protocol.

5.3.2.4.2. Revision of the continuing review timetable.

5.3.2.4.3. Modification of the consent process.

5.3.2.4.4. Modification of the consent document.

5.3.2.4.5. Requirement that additional information be provided to current participants (e.g., whenever the information may relate to the participant's willingness to continue participation).

5.3.2.4.6. Requiring re-consent of current participants

5.3.2.4.7. Requirement that additional information be provided to past participants.

5.3.2.4.8. Require additional training of the investigator and/or study staff.

5.3.2.4.9. Reconsideration of approval.

5.3.2.4.10. Requirement that currents participants re-consent to participation.

5.3.2.4.11. Monitoring of the research.

5.3.2.4.12. Monitoring of the consent process.

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

5.3.2.4.14. Suspension of the research.

5.3.2.4.15. Termination of the research.

5.3.2.4.16. 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 in writing to the *Institutional Official, OHRP, and FDA (if FDA-regulated research).* See policy MHC_RP0111 Suspension, Termination and Investigator Hold.

5.3.2.5.2. If 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:

5.3.2.5.2.1. Notify the *Principal 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

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

5.3.2.5.2.3. Whether further reporting to Refer to other organizational entities or committees if applicable.

5.3.2.5.2.4. Whether notification of current subjects is necessary (e.g., when information might relate to subjects' willingness to continue to take part in the research) –

5.3.2.5.2.5. IRB staff will instruct PI to create Dear subject letter.

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

5.3.2.7. Administrative Reporting Requirements

5.3.2.7.1. Corporate Research Manager or designee will prepare written reports as required by federal regulations, state and local laws, and institutional policies and distribute within applicable time frames through the IRB electronic submission system and federal regulatory reporting process to the:

5.3.2.7.1.1. Primary Investigator and additional individuals (see 5.3.2.5.).

5.3.2.7.1.2. Prepare a report for the IO within fourteen (14) business days of the IRB meeting where it was determined the event constituted an UP.

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

6. References

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

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

6.3. Appendix I *"Definitions"*

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

7. Previous Revisions: 12/3/12, 11/18/13, 11/24/15, 12/15/21

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

9. Approvals:

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

MHC Institutional Review Board acknowledgements: 11/19/13, 12/4/15, 4/14/16

Signature on File *1/31/23*

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Justin Klamerus, MD, MMM Date
Executive Vice President/Chief Medical Officer
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