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Preparing for AAHRPP Re-Accreditation
Guidance for Researchers and Research Staff*

All McLaren Investigators/Researchers, Administrators, HRPP Staff, and IRB Members are essential components of the Human Research Protection Program (HRPP) throughout the corporation and its subsidiary hospitals. The McLaren Human Research Protections Program (HRPP) is currently seeking re-accreditation. AAHRPP accreditation is a gold standard that will contribute to increased interest in the research being performed at McLaren and publicly affirms McLaren as a top-tier institution in ethical and regulatory conduct of human subject research.

The AAHRPP site review team will be at the McLaren Healthcare Corporation on February 16th and 17th. You have been chosen as an individual to be interviewed. The HRPP re-accreditation largely depends on successful completion of these interviews. We are counting on the commitment you make and solicit your help in this endeavor. We have created materials to help you succeed.

Attached Packet includes:

Question to Consider: *Please note that we DON'T know the exact questions that the Site Visitors will ask. This is just a guide to help you prepare.*

This guidance is not intended to be memorized; it is intended to focus your thinking as you prepare for the interview. You may be familiar with the information included however; it is important that you refresh your understanding. Interviews are very collegial and supportive.

AAHRPP Site Visitors:

Robin Ginn, MBA, BSN, CHC, CHRC – Team Leader
Assistant Vice President, Research Administration, Executive Director,
Office for Clinical Research
Emory University

Francis DiMario, MD, CIP, MA
Associate Chair for Academic Affairs, Medical Director HRPP, Chair IRB Pediatrics
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McLaren Health Care Human Research Protection Program (HRPP)

AAHRPP Review Guide for IRB Members

APPLICABLE HRPP REGULATIONS, LAWS, CODES, AND PROTECTIONS

1. What rules or guidelines are you expected to follow?
2. How did MHC transition to the Revised Common Rule?
3. What ethical standards or guide does the IRB follow?
4. What is an example of how the IRB applies the Belmont Principles?
5. What is the process for determining whether an activity is under the purview of the IRB?
6. What is meant by “Equivalent Protections?”
7. How does MHC ensure the rights and welfare of participants are protected when the investigator is operating at a non-MHC facility, is conducting collaborative research, or when oversight is shared with or deferred to another organization or IRB?
8. When would an institution be considered “engaged” in research?

SCIENTIFIC/DISCIPLINARY EXPERTISE AND REPRESENTATIVE CAPACITY

1. Who serves as the non-scientific members and who serves as the non-affiliated members of the IRB?
2. Who is involved in conducting scientific review at McLaren?
3. Does the IRB ever require consultations when reviewing research and when would a consultant be required?

CONFLICT OF INTEREST (COI)

1. What is MHC’s policy on Research Conflict of Interest (COI)?
2. How does the IRB manage researcher COI?
3. Who has the ultimate authority regarding management of investigator conflict of interest?
4. How is IRB member conflict of interest identified and handled at a meeting?

INSTITUTIONAL SUPPORT

1. Who is ultimately responsible for the HRPP?
2. How is authority communicated to the research community?
3. Who has the authority to approve research? Can decisions be overturned?

RESOURCES AND EDUCATION

1. How does the IRB learn of new or revised policies/procedures/regulations?
2. What type of onboarding and ongoing training is provided?

QUALITY IMPROVEMENT, PERIODIC REVIEW OF HRPP & IRB PERFORMANCE EVALUATION

1. What kinds of research compliance or quality improvement reporting is conducted?
2. Is your performance as an IRB member periodically evaluated?
3. Are the IRB members given feedback about the evaluation?
4. What is the process to submit suggestions, concerns, and questions regarding administrative, operational issues?

IRB APPOINTMENT, OPERATIONS, AND GENERAL REVIEW CONCEPTS

1. How easy is it to bring up questions and concerns at the meeting regarding a review being conducted?
2. What does the IRB consider when evaluating whether recruitment materials/advertisements are appropriate?
3. How does the IRB determine if approval criteria are met?
4. Name a specific study design that can be ethically challenging for the IRB?
5. What is the difference between protecting the privacy interests of participants and maintaining the confidentiality of data?

CONSIDERATIONS FOR INITIAL REVIEWS, CONTINUING REVIEW, MODIFICATIONS

1. What is a controverted issue? Describe a controverted issue that came up at a meeting, the different points of view, and how the issue(s) was/were resolved.
2. What criteria are used by the IRB to determine when a modification needs full review?
3. What is a Specific Finding?
4. How does the IRB evaluate the investigator's plan for managing information that could affect the subjects' willingness to continue participation?

EXEMPT DETERMINATION

1. Who has authority at McLaren to make exempt determinations?

EXPEDITED REVIEW PROCEDURES

1. Who can conduct expedited review?
2. Under what circumstances can the IRB utilize expedited procedures to review a proposed change to previously approved research?

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1. What are the types of risk the IRB should consider?
2. What factors are considered when interpreting Minimal Risk?
3. How does the IRB determine whether the risks are reasonable in relation to the potential benefits?
4. What outcomes may be impacted by risk classification?
5. What is the MHC IRB's criteria for requiring a data and safety monitoring plan?
6. What is considered in evaluating a data and safety monitoring plan?

NON-COMPLIANCE, SUSPENSION, OR TERMINATION OF RESEARCH

1. How does the IRB decide non-compliance, serious, or continuing non-compliance?
2. What is the difference between suspension and termination?
3. What is the MHC IRB's purview in terms of suspending or terminating protocols?

INVESTIGATOR REPORTING REQUIREMENTS & UNANTICIPATED PROBLEMS INVOLVING RISK

1. What are some types of events/issues that investigators report to the IRB?
2. What types of events/issues are investigators required to PROMPTLY report to the IRB?
3. How does the MHC IRB define an Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)?
4. Why are there so few events or problems that meet the threshold of a true UPIRSO?

IRB REPORTING REQUIREMENTS

1. What is IRB's reporting requirements?
2. How do MHC comply with the requirements?
3. What MHC report to Regulatory Authority?
4. Content of the IRB findings
5. AAHRPP reporting Requirements

VULNERABLE POPULATIONS

1. Who is vulnerable?
2. Vulnerable to what?
3. How does regulation address vulnerability?
4. IRB review of vulnerability

INFORMED CONSENT

1. Why Informed Consent?
2. What are Elements of Informed Consent?
3. Challenges with Informed Consent Process
4. When can we waive Informed consent requirement?
5. Under Common Rule General waivers and alterations
6. FDA regulations for exception from Informed Consent

FDA REGULATED RESEARCH

1. Is your Research FDA Regulated? When do the FDA regulations apply?
2. When IND is not require?
3. How FDA handles "Off Label" use of drug, device or biologics?
4. FDA Exemption from IRB review
5. What is the IRB's role in reviewing FDA regulated research?
6. What is Form 1572?
7. What happens when you need to use a test article in a life threatening situation (single subject emergency use)?

COMMUNITY BASED PARTICIPATORY RESEARCH (CBPR)

1. What is CBPR?
2. IRB Review of CBPR studies
3. Improving IRB approach towards CBPR studies

COMMUNICATION AND OUTREACH TO CURRENT AND PROSPECTIVE RESEARCH PARTICIPANTS

1. Goals of Participant communication and Outreach Program?
2. Why Research communication is so important?
3. Where can I find outreach resources and Educational Materials?
4. Who manages the outreach program at MHC?

APPLICABLE HRPP REGULATIONS, LAWS, CODES, AND PROTECTIONS

1. What rules or guidelines are you expected to follow?

Federal Regulations that Apply to All MHC Human Subject Research

Department of Health and Human Services (DHHS) 45 CFR 46:

- Subpart A – "Common Rule" IRB Operations, Approval Criteria, Informed Consent
- Subpart B - Fetuses/Pregnant Women/Neonates
- Subpart C – Prisoners
- Subpart D – Children

Regulations that are Applicable to Select Protocols

- Food and Drug Administration regulations
- Health Insurance Portability Accountability Act (HIPAA), Family Educational Rights and Privacy Act (FERPA) or General Data Protection Regulation (GDPR)

Funding Agency Requirements

- Department of Defense (DoD)
- US Department of Education (DoED)
- Environmental Protection Agency (EPA)
- US Department of Justice (DOJ); National Institute of Justice (NIJ); Bureau of Prisons (BOP)
- Department of Energy (DOE)

State Law or Local Policy

- State laws regarding legally authorized representatives
- Department of Corrections (DOC) consent requirements
- School District Research Review requirements

McLaren Policies, Procedures, and Regulations

- Corporate Level Administrative Regulations:
  - MHC_CC0109: Conflict of Interest Disclosures and Business Integrity
  - MHC_CC1101: Use and Disclosure of Protected Health Information (PHI) – General
  - MHC_CC1111: HIPAA – Uses and Disclosures of PHI for Research
- Executive Vice President/Chief Medical Officer (Institutional Official of Research): Human Research Protections Program Manual
- IRB/Research Integrity Department Policies and Procedures:
  - **Overview of Human Protections Program**
    - Appendix I Definitions
    - MHC_RP0201 Human Research Protections Program
    - MHC_RP0202 Research COI Committee Procedures
  - **IRB Governance and Operations**
    - MHC_RP0101 Authority of the IRB
    - MHC_RP0102 FWA & IRB Registration
    - MHC_RP0103 IRB Membership
    - MHC_RP0104 Determination of Human Subject Research
    - MHC_RP0114 IRB Documentation and Research Record Retention
    - MHC_RP0124 Reporting to Regulatory Agencies and Institutional Officials
    - MHC_RP0126 Conflict of Interest for IRB Members

- **IRB Review Process**
  - MHC_RP0104 Determination of Human Subject Research
  - MHC_RP0105 Exempt Review of Human Subject Research
  - MHC_RP0106 Expedited Review of Human Subject Research
  - MHC_RP0107 Initial Review of Human Subject Research
  - MHC_RP0108 Full Board Review of Human Subject Research
  - MHC_RP0109 Criteria for Approval of Human Subject Research
  - MHC_RP0110 Additional Consideration during IRB Review and Approval
  - MHC_RP0111 Study Suspension, Termination, and Investigator Hold
  - MHC_RP0112 Continuing Review of Human Subject Research
  - MHC_RP0113 Changes to Currently Approved Research
- **Informed Consent**
  - MHC_RP0115 Obtaining Informed Consent from Research Subjects
  - MHC_RP0116 Vulnerable Subjects in Research
- **Operational Guidelines for the IRB**
  - MHC_RP0117 Use of Medical Devices in Human Subject Research
  - MHC_RP0118 Use of Drugs and Biologics in Human Subject Research
  - MHC_RP0119 Expanded Use of Investigational Drugs and Devices
  - MHC_RP0120 Humanitarian Use Device
- **The Research Team**
  - MHC_RP0121 Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)
  - MHC_RP0122 Protocol Deviations, Violations, and Exceptions
  - MHC_RP0123 Non-Compliance in Human Subject Research
  - MHC_RP0125 Investigator Responsibility
  - MHC_RP0128 Relying on an external IRB as an IRB of record

2. How did MHC transition to the Revised Common Rule?

Effective January 21, 2019, the MHC IRB began implementing the new requirements of the Revised Federal Policy for the Protection of Human Subjects, also known as the Common Rule, found in the Code of Federal Regulations at 45 CFR 46.

On January 21, 2019 and thereafter, new protocol submissions to the MHC IRB were required to use updated consent templates which can be found on the IRB website. If a study was approved prior to the 1/21/2019 effective date of the 2018 Common Rule, it remained under the Pre-2018 Common Rule until its next Continuing Review. At that point, it transitioned to the 2018 Common Rule. If a study was approved on or after 1/21/2019, it is automatically governed by the new rule.

See the MHC policy on transitioning to the Revised Common Rule here.

3. What ethical standards or guides does the IRB follow?

The above research regulations are based on the ethical principles set forth in the Nuremberg Code, Declaration of Helsinki, and the Belmont Report issued by the National Commission forthe Protection of Human Subjects 1979. Belmont outlines three ethical principles that are central to human subject protection:

- **Respect for persons** involves recognition of the personal dignity and autonomy of individuals and special protection of those persons with diminished autonomy.
- **Beneficence** entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.
- **Justice** requires that the benefits and burdens of research be distributed fairly.

Remember/Consider….

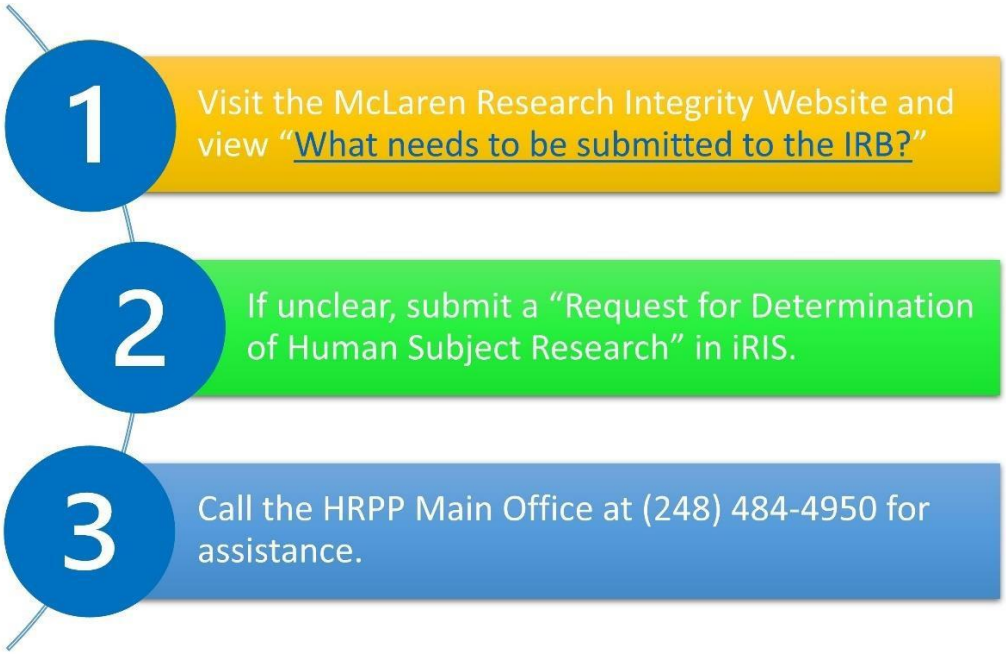
Proposed research that is compliant with the regulations may still have ethical concerns.

Researchers should apply ethical principles and standards appropriately.

4. What is an example of how the IRB applies the Belmont Principles?

- We question if consent process is designed to **respect** subject autonomy and ensure those with diminished autonomy have appropriate protections and safeguards.
- We spend a lot of time on **risk** – benefit analysis, considering risk and benefit to subjects and society; the magnitude and probability of possible harm, and potential efforts to minimize risks. We look to see if the study is designed properly to minimize risk and maximize gain.
- In considering **justice**, we examine the study population and recruitment plan to determine if risks/benefits are distributed fairly and no particular group is being unjustifiably excluded or being targeted for convenience or due to their compromised position.

5. What is the process for determining whether an activity is under the purview of the IRB?



6. What is meant by "Equivalent Protections?"

Equivalent protections are regulatory or ethical systems that exist in countries outside of the United States to protect human research subjects that are ethically equivalent to those in the US. Equivalent protections may include regulation, law, ethical codes, and cultural standards.

Identify Applicable Requirements/Protections: If research is to be conducted at an international location, the investigator identifies local regulations, laws, or standards for human subject protection. The Office for Human Research Protections (OHRP) International Website includes tools for international research including **laws, regulations, and guidelines** from more than 100 countries; and **European General Data Protection Regulation (GDPR) Guidance**.

Cultural Consultation: The IRB obtains a cultural consultant to provide comments, concerns, translations, in writing to the IRB on protocols involving non-English speaking subjects, and/or subjects from a foreign culture.

7. How does MHC ensure the rights and welfare of participants are protected when the investigator is operating at a non-MHC facility, is conducting collaborative research, or when oversight is shared with or deferred to another organization or IRB?

In iRIS, investigators are required to submit a "Request to use an External IRB" application and all the applicable supporting documents to the McLaren IRB before a protocol can be submitted to the external IRB.

If research involves collaboration with any sites and/or personnel outside McLaren, then it is considered multi-site research and IRB reliance issues will need to be addressed. When entering into such a relationship, the McLaren IRB will evaluate whether the external IRB has equivalent human subject protections in place. The external IRB must also meet specific criteria. See policy MHC RP0128 Relying on an external IRB as an IRB of record.

McLaren has procedures to define the responsibilities of collaborating institutions and to coordinate communication among responsible IRBs. A fully executed IRB Authorization Agreement (IAA) is required before McLaren may rely on an external IRB for review. An IAA identifies and describes the respective authorities, roles, responsibilities, and methods of communication between an institution/organization providing the IRB review of research and a participating site relying on the institution/organization.

Federal policies require review by a single IRB for select multi-site research. Studies using an external IRB MUST submit to the MHC IRB.

8. When would an institution be considered "engaged" in research?

When its employees or agents for the purposes of the research project obtain:

(1) data about the subjects of the research through intervention or interaction with them;
(2) identifiable private information about the subjects of the research; or
(3) the informed consent of human subjects for the research.

SCIENTIFIC/DISCIPLINARY EXPERTISE AND REPRESENTATIVE CAPACITY

1. Who serves as the non-scientific members and who serves as the non-affiliated members of the IRB?

We have community members that are both non-scientific and un-affiliated with

McLaren. A non-scientific member must be present to have quorum.

TIP: Other IRB members should know the name of the community members on his/her IRB.

2. Who is involved in conducting scientific review at McLaren?

The Scientific Reviewer's signature confirms the soundness of the research design and the ability of the research to achieve its aims.

The Scientific Reviewer must be someone other than the Principal Investigator (PI).

For Medical Resident and Fellows that are part of MHC Graduate Medical Education Program, the Scientific Reviewer must be:

- Program Director
- Assistant Program Director (if Program Director is the PI)
- Chief Medical Officer (if Assistant Program Director is the PI or if no Assistant Program Director)

The Scientific Reviewer attests that the science is meritorious and deserving of conduct in humans by considering the:

- ✓ validity and utility of science;
- ✓ availability and qualifications of personnel;
- ✓ potential subject population; facilities, and equipment; and
- ✓ availability of ongoing mentoring and guidance.

The IRB considers the scientific study design within context of human subject protection. IRB members draw on their own knowledge and expertise to determine if research procedures are consistent with sound research design and the protocol has potential to yield the expected knowledge. When needed, the IRB seeks consultation from content experts.

3. Does the IRB ever require consultations when reviewing research and when would a consultant be required?

Yes, when the IRB does not have the appropriate expertise for a certain type of research, or for a specific population, consultants with competence in special areas may assist in the review. Need could be related to the protocol (biosafety, radiation safety, etc.), the population (cultural, vulnerable subjects), or protections (information safety). The consultants do not vote with the IRB and do not count toward a quorum at a convened meeting.

CONFLICT OF INTEREST (COI)

1. What is MHC's policy on Research Conflict of Interest (COI)?

McLaren has multiple policies on conflict of interest; one for the Review and Management of Conflict of Interest in Research, one for IRB Members, and one for the Institution itself.

A conflict of interest (COI) occurs when any financial arrangement, situation, or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings.

Examples of financial conflict of interest (FCOI) may include:

- The receipt of personal compensation for consulting activity
- Ownership of equity in publicly or privately held businesses
- Income from intellectual property rights held by the researcher

A significant financial interest is:

- Anything of monetary value;
- Whether or not the value can be readily determined;
- Relates to the "Investigator's professional responsibilities on behalf of the Institution;" or
- Belongs to the Investigator or their spouse or dependent children.

Significant Financial Interests (SFI): **Publicly Traded Entities**

- Aggregate value ≥ $5,000 or 5% ownership (income, stock, or a combination of the two)
- During the past 12 months prior to the disclosure
- Not McLaren salary!

Significant Financial Interests (SFI): **Non-Publicly Traded Entities**

- Aggregate value ≥ $5,000 (income payments only)
- During the past 12 months prior to the disclosure
- Any amount of equity (stock, stock options, or other ownership interest) in an entity such as a start-up company
    - Threshold = $0

Physician Payments Sunshine Act of 2010: Open Payments Database

Each investigator must update the disclosure at least annually during the period covered by the grant, or within 30 days of identifying or acquiring a new SFI.

- Part of the Affordable Care Act
- Manufacturers of drugs, devices, and biologicals that participate in federal healthcare programs (i.e. Medicare & Medicaid)
- Track and report annually to Centers for Medicare & Medicaid Services (CMS)
- CMS posts the reported payments and other transfers of value on its public website

AAHRPP Element III.1.B
Researchers and Research Staff must identify and disclose financial interests according to Organizational policies and regulatory requirements, and, with the Organization, manage, minimize, or eliminate financial conflicts of interest.

2. How does the IRB manage researcher COI?

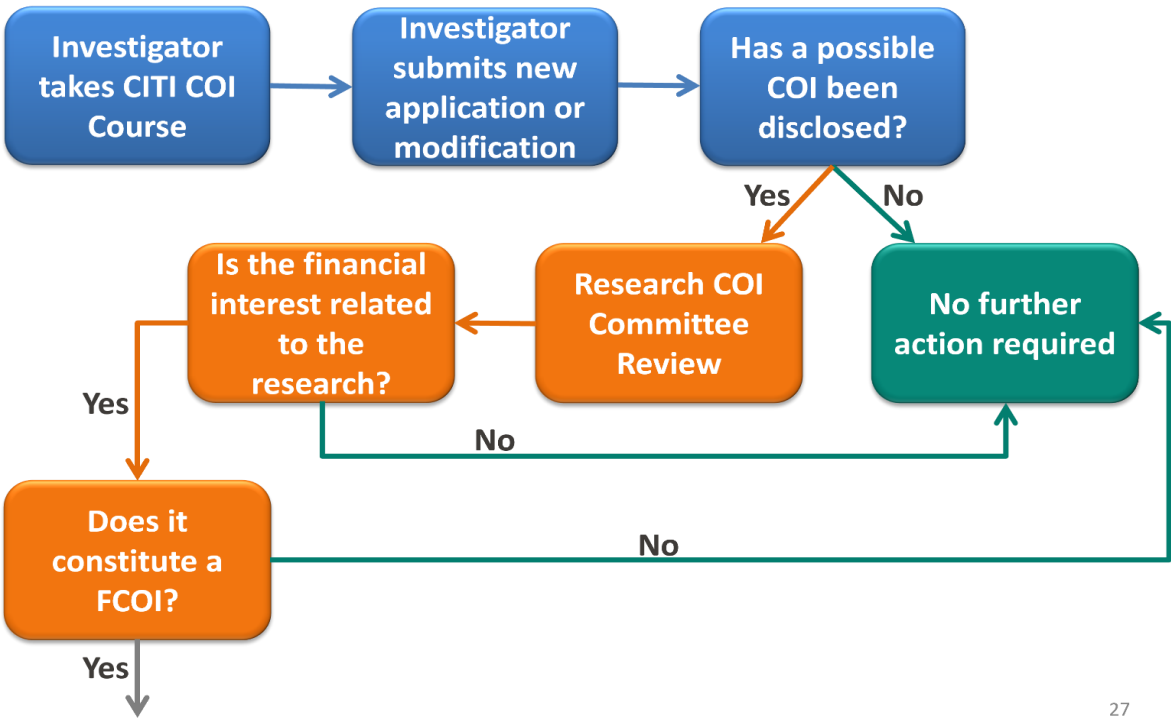
- With mandatory education and training
  - CITI COI Course
- With disclosure of SFIs when the Investigator submits a new protocol to the MHC IRB
  - IRB application asks protocol-specific questions regarding COI

All Investigators are required to adhere to the McLaren Research policy of Review and Management of Conflict of Interest in Research (MHC_RP0202) and must complete Financial Conflict of Interest training. Training is required every 4 years and immediately after:

- McLaren Health Care FCOI policies change in a manner that affects Investigator disclosure/ compliance requirements.
- An Investigator is new to McLaren Health Care or its subsidiary organizations.
- An Investigator is found to be non-compliant with this policy or a specific Management Plan.

The Research Conflict of Interest Committee

- Is the financial interest related to the research?
- If yes, does it constitute a FCOI?
- If a FCOI exists, the Committee will develop a Management Plan.



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1. COI Committee develops a Management Plan and forwards to the IRB for review and approval prior to project implementation.

2. Management Plan is incorporated into the IRB approval letter. PI is notified of management plan at the time of approval and acknowledged plan.

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3. Who has the ultimate authority regarding management of investigator conflict of interest?

After reviewing a significant financial interest in research, the Research Conflict of Interest Committee will communicate its conclusions, along with any management arrangements to be imposed, to the MHC IRB.

For human subject research, the **IRB has the final authority** to decide whether the conflict of interest and approved management plan, if any, allows the research to be approved. The IRB may impose further restrictions on the protocol or disapprove the protocol. The IRB does not have the authority to disapprove the final approved management plan but may require these additional protections.

4. How is IRB member conflict of interest identified and handled at a meeting?

During new IRB member orientation, members are informed about the IRB member Conflicts of Interest policy. At orientation, you are asked to sign a Conflict of Interest agreement indicating that you recognize that the protection of human subjects requires objectivity and you agree to disclose conflicting interests on a protocol by protocol basis. Signed COI Statements are maintained by the MHC IRB.

COI at Convened Meetings:

During convened meetings the IRB Chair prompts members to consider any conflict prior to reviews.

A member with a conflict may be asked questions about the content of the protocol, and issues concerning the study, but must not be present beyond the questions and answers, and, other than to provide information, must not seek, inside or outside the meeting, to influence or affect the voting of non- conflicted members. The minutes must document the fact that the member left the meeting room during the final discussion and vote.

These procedures apply to all types of reviews conducted at a convened meeting (e.g., Initial, Continuing Review, Modification, Unanticipated Problem, etc.).

INSTITUTIONAL SUPPORT

1. Who is ultimately responsible for the HRPP?

Justin Klamerus, MD, Executive Vice President/Chief Medical Officer, is the McLaren IRB Institutional Official (IO) of Research. Dr.Klamerus is the designated IO responsible for oversight and management of all aspects of MHC research.

2. How is authority communicated to the research community?

On the McLaren Research website, the MHC HRPP Manual establishes the authority and independence as well as the level and scope of responsibility for the IRB and describes the organizational structure for human research protection.

McLaren's Human Research Protection Program operates under the authority of the Organization policy "MHC_RP0201_Human Research Protection Program." As stated in that policy, the operating procedures serve as the governing procedures for the conduct and review of all human research conducted under the auspices of the McLaren Health Care Corporation.

3. Who has the authority to approve research? Can decisions be overturned?

The IRB has been granted authority to approve human subject research. If the MHC IRB has DISAPPROVED protocol, no institutional entity may overturn the IRB's determination. MHC and its subsidiary hospitals may review any research protocols and have the right to disapprove the implementation of a research protocol that has been approved by the IRB.

RESOURCES AND EDUCATION

1. How does the IRB learn of new or revised policies/procedures/regulations?

The McLaren Research Integrity website has a Policies page located at https://www.mclaren.org/main/research-policies-procedures. The MHC IRB staff will notify members via email communications, newsletters, or educational sessions during regularly scheduled convened IRB meetings regarding any changes in policies, procedures, or regulations.

2. What type of onboarding and ongoing training is provided?

- **New Members –** CITI Training, PRIM&R EROC, iRIS Training, submissions training.
- **Meeting Educational Sessions –** Brief educational updates on specific topics at the beginning of Convened IRB meetings.
- **Annual IRB Meeting/In-Service** – Education sessions provided once a year to all members including alternates.
- **Medical Ethics Advisor Newsletter** – Topical monthly newsletter with cases, articles, and special interest items

QUALITY IMPROVEMENT, PERIODIC REVIEW OF HRPP & IRB PERFORMANCE EVALUATION

1. What kinds of research compliance or quality improvement reporting is conducted?

- **Directed/For-Cause Review:**
  As part of the McLaren's AAHRPP Quality Improvement and Quality Assurance Program, the Education and Quality Improvement Program (EQuIP) is authorized to perform a directed for-cause audit as requested by the IRB, IRB Chairperson, designee, Institutional Official, or regulatory agency (e.g. FDA, NIH, and OHRP).
- **Routine/Random Review:**

  As part of the McLaren's AAHRPP Quality Improvement and Quality Assurance Program, the Education and Quality Improvement Program (EQuIP) is authorized to conduct QA/QI routine site visits to review research records, observe ongoing research projects, and the consenting process as well as continually educating and updating MHC researchers regarding human subject protection.

  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.
- **Investigator Self-Assessment:**
  The Investigator self-assessment is a tool for researchers to identify gaps, areas for improvement, or education needs.
- **IRB Reviews:**
  These reviews are conducted to measure the effectiveness and/or efficiency of IRB procedures for the protection of human subjects in research. The QI & Education Specialist may periodically conduct a thorough examination of the IRB records, including meeting minutes and approved investigator-initiated research informed consent forms, and/or other materials to evaluate performance and compliance with federal regulations, institutional policy, etc.

2. Is your performance as an IRB member periodically evaluated?

Yes, IRB staff sends all IRB members a Performance Evaluation Questionnaire about once a year. We assess our own performance as well as that of members, chairs, and vice chairs on several attributes such as knowledge, adherence to regulations, attendance, participation, etc.

3. Are the IRB members given feedback about the evaluation?

Yes, we (IRB members and Research Integrity staff) discuss the results in a short phone interview.

4. What is the process to submit suggestions, concerns, and questions regarding administrative, operational issues?

- **IRB Determinations – IRB Chair or Reviewer**

  Investigators may submit a written appeal to the convened IRB, including justification for changing the IRB decision. **The appeal determination is final.**
- At https://www.mclaren.org/main/research-integrity#related-downloads-and-links, you will find a link to the IRB/HRPP Suggestion Box. This sends an email to hrpp@mclaren.org, our departmental mailbox.
- McLaren Health Care has an **anonymous** toll-free hotline which workforce members can use to report potential compliance concerns. Workforce members may contact the MHC Compliance Office at **1-866-MHC-COMPLY**

IRB APPOINTMENT, OPERATIONS, AND GENERAL REVIEW CONCEPTS

1. How easy is it to bring up questions and concerns at the meeting regarding a review being conducted?

Questions and concerns are encouraged!

2. What does the IRB consider when evaluating whether recruitment materials/advertisements are appropriate?

The IRB assures that the advertisements do NOT:

- state or imply a favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
- include claims that the intervention is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device that are inconsistent with Food and Drug Administration (FDA) labeling.
- use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational;
- emphasize rewards or payments;
- include exculpatory language;
- include language implying IRB endorsement (e.g., study is IRB approved);
- promise a certainty of cure beyond what is outlined in the consent and the protocol; or
- promise or imply free medical care rather than specify procedures/care is provided at no cost.

3. How does the IRB determine if approval criteria are met?

- The IRB application forms mirror the regulations so that we get the answers or justifications we need to make determinations.
- The Criteria for Approval Checklist includes informed consent elements and the federally required criteria for approval:
  - Risks to subjects are reasonable in relation to anticipated benefits,
  - Subject selection is equitable
  - Adequate provisions are in place for seeking informed consent (including required and applicable additional elements)
  - The provisions for documenting informed consent/assent are appropriate.
  - Adequate provisions for protecting the privacy and confidentiality of subjects.
  - Safeguards included to protect rights and welfare of vulnerable subjects
  - Data & safety monitoring - Greater than minimal risk research or NIH funded/FDA regulated clinical investigations, adequate provisions are in place for monitoring the data collected
- In addition, the IRB considers other applicable regulatory or protocol-specific requirements (FDA regulated device study, Department of Defense requirements, privacy regulations, etc.) qualifications of research personnel, adequacy of research setting, and signature assurance of chairperson or faculty advisor documenting scientific review.

4. Name a specific study design that can be ethically challenging for the IRB?

- **Cluster randomization** (large group randomization does not allow prospective consent from individuals studied)
- **Comparative Effectiveness** (Standard of Care, but are there risks from randomization itself; if so how can study design mitigate risk and is risk communicated in informed consent?)

- **Digital Device Studies** (Is the device a medical digital device or mobile application (app) that is being tested? Is the device or app being used to collect data? Are the terms of agreement for use of available apps consistent with informed consent confidentiality protections?)

5. What is the difference between protecting the privacy interests of participants and maintaining the confidentiality of data?

Privacy is the freedom from unauthorized intrusion – **the right to be left alone**. In many research settings, privacy translates to the right of a person to control who has access to information about him or her. In clinical research, this usually means that the researcher may not perform any procedures or access any personal information about a person without that person's consent.

Confidentiality is the ability to **keep something secret**. In IRB terms, this relates to an investigator's responsibility to prevent the unauthorized disclosure of information without permission of the research subject. A breach of confidentiality will harm the trust relationship between the subject and the researcher that will be difficult to mend.

Are confidentiality and privacy issues different in research than they are in clinical practice? Probably not. The major difference is that in clinical practice, any invasion of privacy is done for the best interest of the patient, whereas in research, an invasion of privacy is not for the benefit of the subject but is for the advancement of science. Thus, the subject or patient can more easily accept something that is done for his/her benefit than for the benefit of others.

CONSIDERATIONS FOR INITIAL REVIEWS, CONTINUING REVIEW, MODIFICATIONS

1. What is a controverted issue? Describe a controverted issue that came up at a meeting, the different points of view, and how the issue(s) was/were resolved.

A controverted issue is an issue that results in disagreement or opposing viewpoints among IRB members that are discussed during the IRB's deliberations. Regulations require a summary of controverted issues and their resolution to be included in IRB meeting minutes. The IRB discussions should revolve around the ethical and regulatory criteria for IRB approval, including but not limited to the provisions for:

- ✓ Minimizing risk;
- ✓ Informed consent procedures; and
- ✓ Protections against coercion or undue influence.

2. What criteria are used by the IRB to determine when a modification needs full review?

Any modification that is **NOT** deemed **minor** by the primary reviewer is subject to review by the IRB at a convened meeting. Minor modifications are considered eligible for expedited review. According to MHC Research Integrity policy definition, a minor change is one which makes **NO** substantial alteration in:

- ❖ The level of risk to subjects;
- ❖ The research design or methodology (adding procedures that are not eligible for expedited review would not be considered a minor change);
- ❖ The number of subjects enrolled in the research (no greater than 10% of the total requested);
- ❖ Qualifications of the research team;
- ❖ The facilities available to support the safe conduct of the research; or
- ❖ Any other factor which would warrant review of the proposed changes by the convened IRB.

Additional considerations may include substantial alterations to:

- ❖ The informed consent process/documentation;
- ❖ Safety and monitoring of subjects;
- ❖ Privacy or data confidentiality; or
- ❖ The subject selection/population.

Please also review MHC Research Integrity policy MHC RP0113 Changes to Currently Approved Research.

3. What is a Specific Finding?

Specific findings are the **specific regulatory criteria** that must be addressed for the IRB to make regulatory determinations.

IRB Forms mirror regulations by asking for information to address each criterion that must be met for the IRB to make a specific finding.

Examples of IRB specific findings and select regulatory criteria may include:

- ❖ Waiver or Alteration of Informed Consent
- ❖ Waiver of Documentation of Informed Consent
- ❖ Medical Devices

- ❖ Pregnant Women, Fetuses, and Neonates
- ❖ Children

4. How does the IRB evaluate the investigator's plan for managing information that could affect the subjects' willingness to continue participation?

Some IRB forms (CR, UPIRSO) prompt the reviewer to consider significant new findings that might relate to the subjects' willingness to continue participation.

Notification vs. Re-Consent

The reviewer documents if the PI's proposal for communicating the information is appropriate and if not, describes revisions needed. The IRB evaluates the significance of the information in determining what course of action is appropriate **(notification or re-consent)**.

In the case of a UPIRSO, MHC Research Integrity policy MHC_RP0121 (UPIRSO) states that if the IRB finds that the event is an unanticipated problem involving risks to participants or others, the IRB may recommend any of the following actions including, but not limited to:

- ❖ Requiring modifications to the protocol.
- ❖ Revising the continuing review timetable.
- ❖ Modifying the consent process or document.
- ❖ Providing additional information to current participants (e.g., whenever the information may relate to the participant's willingness to continue participation).
- ❖ Providing additional information to past participants.
- ❖ Requiring additional training of the investigator and/or study staff.
- ❖ Reconsidering approval.
- ❖ Requirement that current participants re-consent to participation.
- ❖ Monitoring of the research or the consent process.
- ❖ Referral to other organizational entities (e.g., legal counsel, risk management, institutional official).
- ❖ Suspending the research.
- ❖ Terminating the research.

EXEMPT DETERMINATIONS

1. Who has authority at McLaren to make exempt determinations?

The MHC IRB has the authority to make exemption determinations (not investigators). That is, the MHC IRB is responsible for determining whether a research activity is exempt from 45 CFR 46 and 21 CFR 56.

Determination of whether human subject research can be exempt is made by the MHC IRB Chair, designee, or IRB Analyst who is also a member of the IRB, acting on behalf of MHC IRB.

Investigators or others within the organization may not make exemption determinations.

Human subjects research studies determined to be exempt are conducted in a manner consistent with the ethical principles set forth by the Belmont Report.

The IRB chair or designee is subject to MHC Research Integrity policy MHC_RP0126 Conflict of Interest for IRB Members when reviewing and making exemption determinations.

MHC IRB members are notified of exempt determinations at the time of the fully convened meeting. Studies meeting the exempt criteria are reported on the agenda as informational only and are also documented in the meeting minutes.

Additional resources provide guidance regarding issues to address in determining when studies are exempt from regulations.

- ✓ **Will there be interactions with patients?**

  If yes, the reviewer should determine whether there should be a consent process that will disclose information describing the research, procedures, the voluntary nature of participating, and contact information.

- ✓ **Will a request be made for a waiver of individual HIPAA authorization or alteration of Individual HIPAA authorization?**

  If yes, a privacy officer, who is also a member of the MHC IRB, will be assigned as a reviewer.

- ✓ **Do exempt projects require continuing review?**

  No! Once a research project is determined to be exempt, it is not reviewed again unless a change is proposed and a modification is submitted (except when the exempt study requires limited IRB review).

  There is no continuing review process for exempt research, as long as the criteria for exemption remain satisfied (and are not subject to limited IRB review).

The IRB may determine that continuing review is required for a study subject to limited IRB review, in which case it will document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

✓ **Exempt studies are administratively closed once the stated end date that is listed in the approval letter arrives.**

Summary of Exempt Categories	
1	Teaching/educational setting.
2	Surveys, tests, and interviews.
3	Benign behavioral intervention.
4	Record review/secondary research.
5	Federal agencies projects.
6	Taste, food, and consumer acceptance studies.

**Exempt Categories 7 & 8 are not adopted by MHC and are not listed here.*

EXPEDITED REVIEW PROCEDRES

1. Who can conduct expedited review?

The IRB chairperson or one (or more) experienced and trained members.

The expedited reviewer considers same approval criteria as full board. Research must be minimal risk an all procedures fit one or more expedited categories.

2. Under what circumstances can the IRB utilize expedited procedures to review a proposed change to previously approved research?

Please review MHC Research Integrity policy MHC_RP0106 Expedited Review of Human Subject Research for detailed information.

Typically:

- ✓ No more than minimal risk submissions (includes most modifications and final reports)
- × New studies that are expedited are **very rare** (most are exempt or full board)
- × Suspensions, terminations, or disapprovals

Summary of Expedited Categories	
1	Clinical studies of drugs and medical devices only when certain conditions are met.
2	Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture in certain populations and within certain amounts.
3	Prospective collection of biological specimens for research purposes by noninvasive means.
4	Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves.
5	Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes.
6	Collection of data from voice, video, digital, or image recordings made for research purposes.
7	Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

**Expedited Categories 8 & 9 apply to Continuing Reviews only and are not listed here.*

RISK ASSESSMENT AND SAFETY EVALUATION

1. What are the types of risk the IRB should consider?

The IRB should consider a wide range of categories regarding types of risks. For example, **risks can be physical, psychological, social, economic, legal, or unknown.**

Risks can apply to **individuals or may apply to classes of participants** (e.g., research on alcoholism in Native Americans).

IRB reviewers should be diligent to focus only on the risks associated with the protocol that are **directly related to the research,** (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).

The IRB should concentrate on the **immediate or reasonably foreseeable risks** of the research rather than the risks associated with the long-term outcome or consequences of applying the knowledge gained from the research.

2. What factors are considered when interpreting Minimal Risk?

The IRB considers **probability** or **magnitude** of harm from the research, relative to the general (healthy) population.

- **Probability** of harm
- **Magnitude** of harm
- Efforts to minimize risks

Question for consideration: Which people's daily lives should serve as the baseline for determining when research risks are minimal?

- Risks that the people enrolled in the study experience?
- Risks that average, healthy, "normal" people experience during the course of daily life?

3. How does the IRB determine whether the risks are reasonable in relation to the potential benefits?

The IRB first identifies potential risks. The IRB considers both **probability** and **magnitude** of harm and discomfort associated with the risk.

The IRB then identifies potential benefit. **The benefits of a study do not negate or alter the level risk.**

The IRB then assesses whether risks to participants are **reasonable** in relation to the anticipated benefits to participants and importance of knowledge expected to result.

The MHC Risk/Benefit Assessment is described in detail in Section 5 of MHC Research Integrity policy MHC_RP0109 Criteria for Approval of Human Subject Research.

4. What outcomes may be impacted by risk classification?

The risk classification may influence many factors including, but not limited to:

- the mode of review (expedited vs. full board);
- whether or not a protocol can be approved by the IRB;
- the need for a data and safety monitoring plan;
- the frequency of review; and
- consent requirements (one of the criteria for waiver is "minimal risk").

5. What is the MHC IRB's criteria for requiring a data and safety monitoring plan?

The MHC IRB requires review and approval of data and safety monitoring plans for all research that is more than minimal risk. For these studies, the investigator must submit a safety monitoring plan.

Also, some NIH funded clinical investigations or FDA regulated clinical investigations require a Data and Safety Monitoring Board (DSMB).

In general, it is desirable for a DSMB to be established by a study sponsor for research that is:

- ✓ blinded;
- ✓ involves multiple sites;
- ✓ involves vulnerable subjects; or
- ✓ employs high-risk interventions.

6. What is considered in evaluating a data and safety monitoring plan?

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

- ✓ Monitoring is commensurate with the nature, complexity, size**,** and risk involved.
- ✓ Monitoring is timely. Frequency should be commensurate with risk.
- ✓ Conclusions are reported to the IRB.
- ✓ For low-risk studies, continuous, close monitoring by the study investigator or an independent Individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies as appropriate.

NON-COMPLIANCE, SUSPENSION OR TERMINATION OF RESEARCH

1. How does the IRB decide non-compliance, serious, or continuing non-compliance?

Non-compliance is defined as conducting research in a manner that disregards or violates federal regulations or institutional policies and procedures applicable to human research. It is a failure to follow the regulations or the requirements or determinations of the MHC IRB.

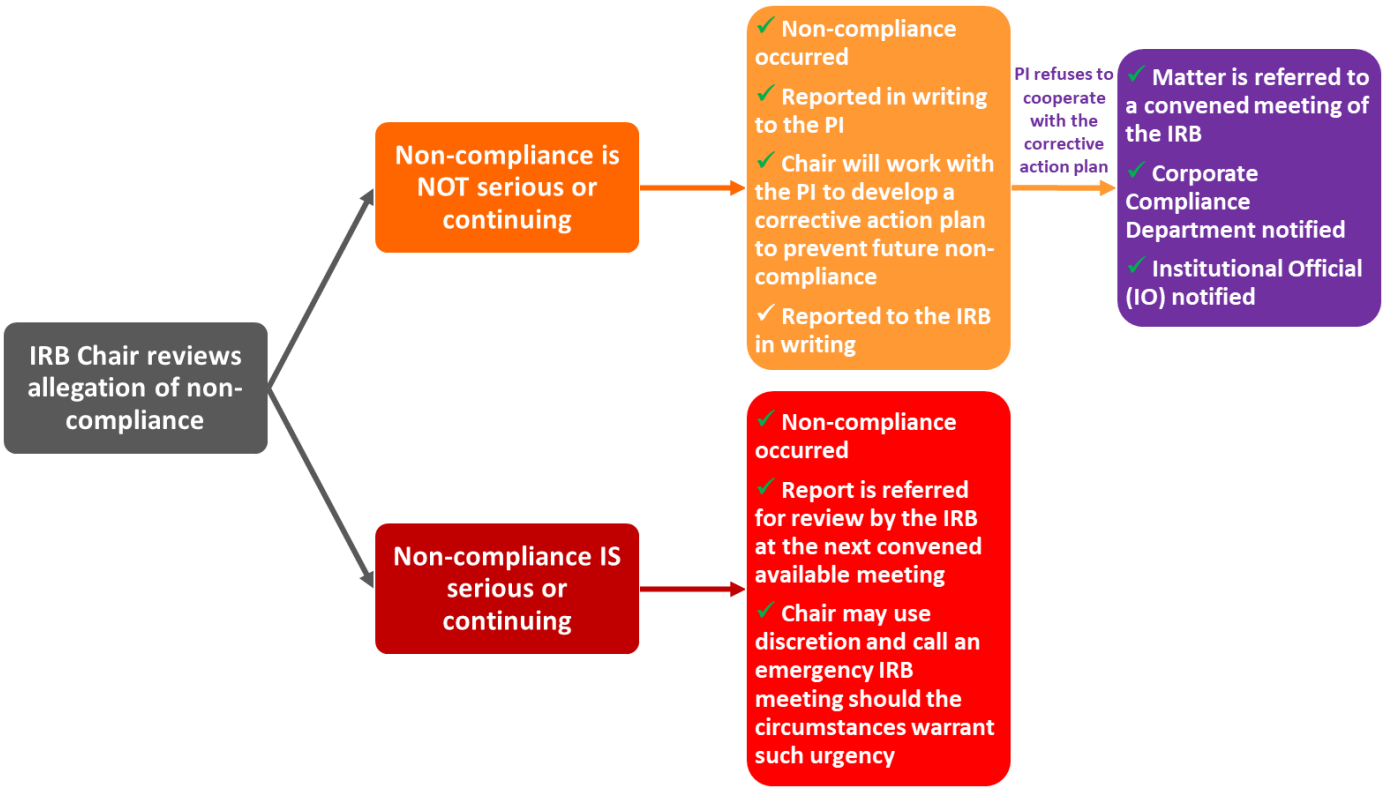
Non-compliance with IRB policies and/or federal requirements may involve a range of issues from relatively minor, administrative, or technical violations to more serious violations which pose risk to subjects and/or violations of their rights and welfare.

All allegations of non-compliance are reviewed by the IRB Chair.

Continuing non-compliance is a pattern on 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.

Serious non-compliance is non-compliance that adversely affects the rights and welfare of subjects.

Please review MHC Research Integrity policy MHC RP0123 Non-Compliance in Human Subject Research For more details.



2. What is the difference between suspension and termination?

A **suspension** is the **temporary** interruption in the enrollment of new subjects, activities involving previously enrolled subjects, or other research activities.

A **termination** is a **permanent** halt in the enrollment of new subjects, activities involving previously enrolled subjects, or other research activities.

3. What is the MHC IRB's purview in terms of suspending or terminating protocols?

MHC Research Integrity policy MHC RP0111 Study Suspension, Termination, and Investigator Hold states the following:

The IRB Chair is responsible for determining if immediate actions are needed to protect the rights and welfare of study subjects prior to the item(s) being reviewed by the next available fully convened IRB.

The IRB is responsible for suspending or terminating currently approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

INVESTIGATOR REPORTING REQUIREMENTS & UNANTICIPATED PROBLEMS INVOLVING RISK

1. What are some types of events/issues that investigators report to the IRB?

- ✓ Adverse Events (AE) and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)
- ✓ Protocol Deviations, Violations, and Exceptions – any change which occurred WITHOUT prior IRB review and approval
- ✓ Protocol non-compliance, suspension, or termination
- ✓ Data and Safety Monitoring Reports
- ✓ FDA Correspondence
- ✓ Subject Complaints that require IRB involvement
- ✓ Audit, Inspection, or Inquiry by a Federal or External Agency

2. What types of events/issues are investigators required to PROMPTLY report to the IRB?

Prompt reporting is required for:

- ❖ **Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)**
  - ➢ Including IND Safety Reports from Sponsors
- ❖ **Adverse Events (AE)** involving direct harm to participants (either local or external) which in the opinion of the Principal Investigator meets the criteria for a UPIRSO
- ❖ **Local Deaths**, 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
  - ➢ Deaths from minimal risk studies such as registries should be reported at Continuing Review (Unless the death meets all 3 criteria of UPIRSO: **Unexpected, Related, Serious**)
- ❖ **New information** that indicates a change to the risks or potential benefits of the research
- ❖ **A breach of confidentiality**
- ❖ **Incarceration** of a participant in a protocol not approved to enroll prisoners

3. How does the MHC IRB define an Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)?

Unanticipated problems involving risks to participants or others (UPIRSO) refer to any incident, experience, outcome, or new information that:

1) 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.
2) Is **related or possibly related** to participation; that is, there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.
3) Is **serious**, such that 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.

4. Why are there so few events or problems that meet the threshold of a true UPIRSO?

Most adverse events are not true UPIRSO because they were anticipated, expected, or listed in the consent; were unrelated to participation in the research; or were not serious or did not suggest that the research involves greater risk of harm.

IRB REPORTING REQUIREMENTS

1. What is IRB reporting requirements?

The regulations often do not provide clear, concise definitions. Having been drafted with some flexibility in mind, the regulations provide a general framework for protecting human subjects.

Both HHS and FDA regulations require that IRBs maintain written procedures ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head (such as OHRP or FDA) of any unanticipated problems involving risks to subjects or others.

OHRP (2007) Guidance	FDA (2009b) Guidance
Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events	Guidance for Clinical Investigators, Sponsors, and IRBs; Adverse Event Reporting to IRBs - Improving Human Subject Protection

2. How do MHC comply the requirements?

MHC has Comprehensive policies and procedures for reportable events which include:

- Processes to follow in reporting to the IRB
- How the IRB office handles the reports
- The IRB review process and required determinations
- Possible remediation options
- Further reporting requirements and processes

Refer MHC_RP0124 Reporting to Regulatory Agencies and Institutional Officials

3. What MHC IRB report to Regulatory authority?

It is the policy of the IRB to comply with all applicable local, state, and federal regulations that require the following to be reported to the appropriate Institutional Official, the federal agency head or the FDA as applicable.

The MHC IRB is responsible for promptly reporting on behalf of all MHC subsidiary hospitals:

- ❑ Any **unanticipated problems involving risks** to subjects or others;
- ❑ Any **serious or continuing noncompliance** with Department of Health and Human Services (DHHS) or FDA regulations as applicable;
- ❑ Any **suspension or termination of MHC IRB-approved non-exempt human subjects research** to the applicable institutional officials and as required or appropriate, to the applicable regulatory agencies. (within 30 days)

Institutional Official can suspend/terminate the researchers and/or research at any McLaren subsidiary hospitals.

4. Content of the Report of IRB findings

At a minimum, the following information should be included in the report of IRB findings:

- ❑ Name of the institution conducting the research;
- ❑ Title of the associated research project and/or grant proposal;
- ❑ Name of the principal investigator on the corresponding research protocol;
- ❑ Number assigned by the MHC IRB to the research project and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
- ❑ A detailed description of the reason for the report;
- ❑ Actions taken by the institution to address the reported issue.

5. AAHRPP Reporting Requirements

In order to maintain accreditation, an organization completes a report and files it with AAHRPP annually until an Application for Reaccreditation is submitted.

- ➢ Who is responsible for Reporting?
  - Research QI Compliance and Education Specialist
  - Researchers
  - IRB
- ➢ To whom to Report

  Corporate Manager of Research and Integrity or designee
- ➢ What to report and when to Report

  https://www.aahrpp.org/accreditation/maintain-accreditation/required-reports

Within 48 hours:

Any negative actions by a government oversight office, including but not limited to OHRP Determination Letters

FDA Warning Letters,

FDA 483 inspection reports with official action indicated,

FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken related to human research protections.

Any legal dispute

litigation

Arbitration

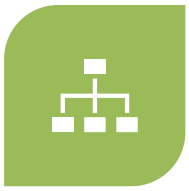
settlements initiated related to MHC's human research programm;

Any negative press covering

Like radio, TV, newspaper, online publications of a negative nature regarding MHC's human research protections program.

Within 30 Days:

WHEN MHC OR ITS HUMAN RESEARCH PROTECTION PROGRAM HAS A SUBSTANTIVE CHANGE



IN CORPORATE STRUCTURE

A CHANGE OF OWNERSHIP OR LEADERSHIP

A CHANGE OF NAME

Annual Report:

Organizational Changes

Changes in Resources

Changes in Program Scope

Addition, removal, or modification of functions, committees, or IRBs.

Changes in method of providing services, such as use of external IRBs or contracting for services from another organization.

Catastrophic event that results in an interruption or discontinuance in a part of or the entire Human Research Protection Program.

VULNERABLE POPULATION

- Jewish Chronic Disease Hospital Study
- U.S. Public Health Service (PHS) Syphilis Study at Tuskegee
- Nazi Medical Experiments
- Gene Therapy study
- Willowbrook Hepatitis Study

The National Bioethics Advisory Committee (NBAC 2001) defines vulnerable subjects as persons who "have difficulty providing voluntary, informed consent arising from limitations in decision-making capacity…or situational circumstances…or because they are especially at risk for exploitation."

Type of Vulnerability	
1	Cognitive or communicative
2	Institutional
3	Medical
4	Economic
5	Social
6	Deferential

1. Who is Vulnerable?

Pregnant women	Human fetuses	Neonates	Prisoners
Children	Individuals with physical disabilities	Individuals with mental disabilities or cognitive impairments	Economically disadvantaged
Socially disadvantaged	Terminally ill or very sick	Racial or ethnic minorities	Institutionalized persons (for example, persons in correctional facilities, nursing homes, or mental health facilities)

2. Vulnerable to what?

Type of Abuse:
Physical control
Coercion
Undue influence
Manipulation

3. How does Regulation address vulnerability?

In the U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46 (Protection of Human Subjects 2018), has additional subparts designed to provide extra protections for vulnerable populations which also have additional requirements for IRBs. https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46?toc=1

- Subpart B - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D - Additional Protections for Children Involved as Subjects in Research

The U.S. Food and Drug Administration (FDA), provides a similar list of vulnerable subject examples.

- 21 CFR 56.111(b) Criteria for IRB approvals https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-56/subpart-C/section-56.111
- 21 CFR 50 sub part D Additional safeguards for children in clinical Investigation https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-50/subpart-D

4. IRB review of vulnerability

Are subjects vulnerable?

Is inclusion of vulnerable subjects appropriate?

Are vulnerable subjects adequately protected?

Initial Review of Research Proposal

The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.

The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.

The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.

The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

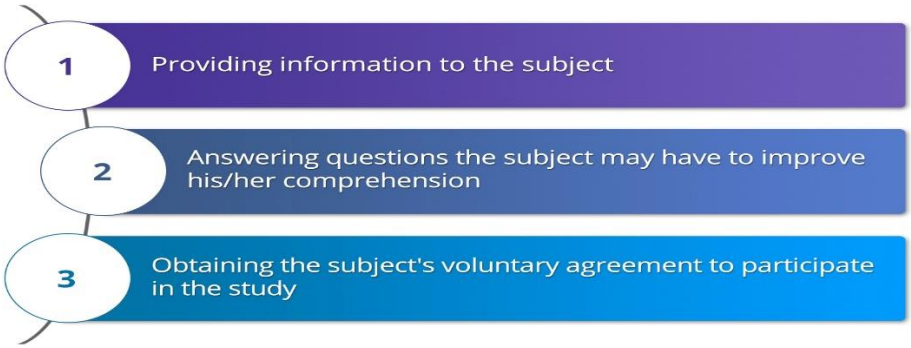
The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.

The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.

- At Continuing Review, the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.
- IRB evaluate the incidence and determine

INFORMED CONSENT

1. Why Inform Consent needed?



The framework for informed consent can be found at

- **45 CFR 46.116(a) (Protection of Human Subjects 2018) and**
- **21 CFR 50.25(a) (Protection of Human Subjects 2015).**

Keep in mind...
Inform consent is not just a form....its a process

2. What are the Basic Elements of Inform Consent?

- A statement that the **study involves research**, an explanation of the research's **purposes** and the expected **duration** of the subject's participation, a description of the **procedures** to be followed, and identification of any procedures that are experimental.
- A description of any reasonably foreseeable **risks or discomforts** to the subject.
- A description of any **benefits** to the subject or to others that may reasonably be expected from the research.
- A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which **confidentiality of records** identifying the subject will be maintained
- For research involving more than minimal risk, an explanation as to whether any **compensation** and an explanation as to whether any medical treatments are available **if injury occurs** and, if so, what they consist of, or where further information may be obtained.
- An explanation of **whom to contact** for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that **participation is voluntary**, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- One of the following statements about any research that involves the **collection of identifiable private information** or identifiable biospecimens:
    1. A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
    2. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

3. What are challenges with Inform Consent Process?

4. When can IRB Waive Inform Consent requirement?

HHS regulations at 45 CFR 46.116 (Protection of Human Subjects 2018) allow an IRB to waive or alter (change the requirements) for informed consent under the following circumstances:

1. Government projects
2. General waivers and alterations
3. Screening, recruiting, or determining eligibility

FDA regulations do not provide for waivers of informed consent except in certain emergency situations

5. Under Common Rule General Waivers and Alterations

General waivers and alterations are permissible if the IRB determines that:

- The research involves no more than minimal risk to subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

6. FDA Regulations for Exceptions from Informed Consent

FDA at 21 CFR 50.23 and 50.24 (Protection of Human Subjects 2015) provides exceptions to the requirement for informed consent under the following circumstances:

- In situations where requirements for exception from informed consent are met for emergency research.
- In life-threatening conditions involving an individual subject where requirements for an exception from informed consent are met and include documentation of all of the following:
  - The researcher, with the concurrence of another physician, believes the situation necessitates the use of a test article (an investigational drug, device, or biologic).
  - The subject and/or LAR is unable to communicate consent.
  - A LAR is "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research" (Protection of Human Subjects 2015).
  - There is insufficient time to obtain consent.
  - No alternative exists that will provide an equal or better chance of saving the subject's life.

FDA Guidance on Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

On 24 July 2017, the FDA issued guidance that they will not object if an IRB approves a waiver or alteration of consent for a no more than minimal risk clinical investigation if the IRB determines that (FDA 2017):

- ❑ The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k)or 56.102(i)) to subjects;
- ❑ The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- ❑ The clinical investigation could not practicably be carried out without the waiver or alteration; and
- ❑ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA REGULATED RESEARCH

1. Is Your Research FDA Regulated? WHEN DO THE FDA REGULATIONS APPLY?

FDA regulations apply to research that involves an FDA-regulated test article in a clinical investigation involving human subjects as defined by the FDA regulations.

Test Article: drugs, biologics, devices, diagnostics, and in some cases dietary supplements and food additives.

For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy, 45 CFR 46 and other regulations must also be applied.

Investigational Drug	IND Application	21 CFR Part 312
Investigational Device	IDE Application	21 CFR Part 812

Please refer to IRB checklist for FDA determination:
Review Checklist 010 - FDA Determination Checklist

2. When IND is not required?

In the regulations at 312.2(b) the clinical investigation of a marketed drug does not require an IND if all of the following conditions are met:

- The data will not be used to support a new indication, new labeling, or significant change in advertising.
- The research does not involve change to the route of administration or dosage level, subject population usage, or other factors that significantly increases the drug product's risks of harm (or decreases the acceptability of the risks).
- The research is conducted in compliance with IRB review in 21 CFR 56 and informed consent requirements in 21 CFR 50 (Protection of Human Subjects 2018).
- The research is conducted in compliance with requirements for promotion and sale at 21 CFR 312.7.

Exemption from IND submission requirements does not mean exemption from IRB review and approval or from the requirement to obtain subjects' informed consent.

3. How FDA handles "Off Label" Use of Drugs, Devices, and Biologics handles?

Why might an approved drug be used for an unapproved use?

What are examples of unapproved uses of approved drugs?

Questions you may want to consider

4. FDA EXEMPTIONS from the requirements of FDA regulations for IRB review

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. [21 CFR §56.104(d)]

5. What is the IRB's role in reviewing FDA regulated research?

In addition to conducting the IRB and informed consent review according to FDA regulations, the IRB has been given specific responsibilities for:

- reviewing the qualifications of investigators,
- assessing the adequacy of research sites, and
- verifying the sponsor's or sponsor-investigator's determination of whether an Investigational New Drug (IND) or Investigational Device Exemption (IDE) is required.

If the IRB is unsure regarding the sponsor or sponsor-investigator's determination regarding need for an IND/IDE, investigators may be required to consult the FDA for a ruling.

6. What is Form FDA 1572?

- Personally conduct or supervise investigation
- Follow protocol
- Ensure all persons assisting is study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)
- Maintain adequate and accurate records and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

7. What happens when you need to use a FDA regulated test article in a life-threatening situation?

- ❑ Emergency use of FDA regulated Investigational drug
- ❑ Emergency use of FDA regulated devices

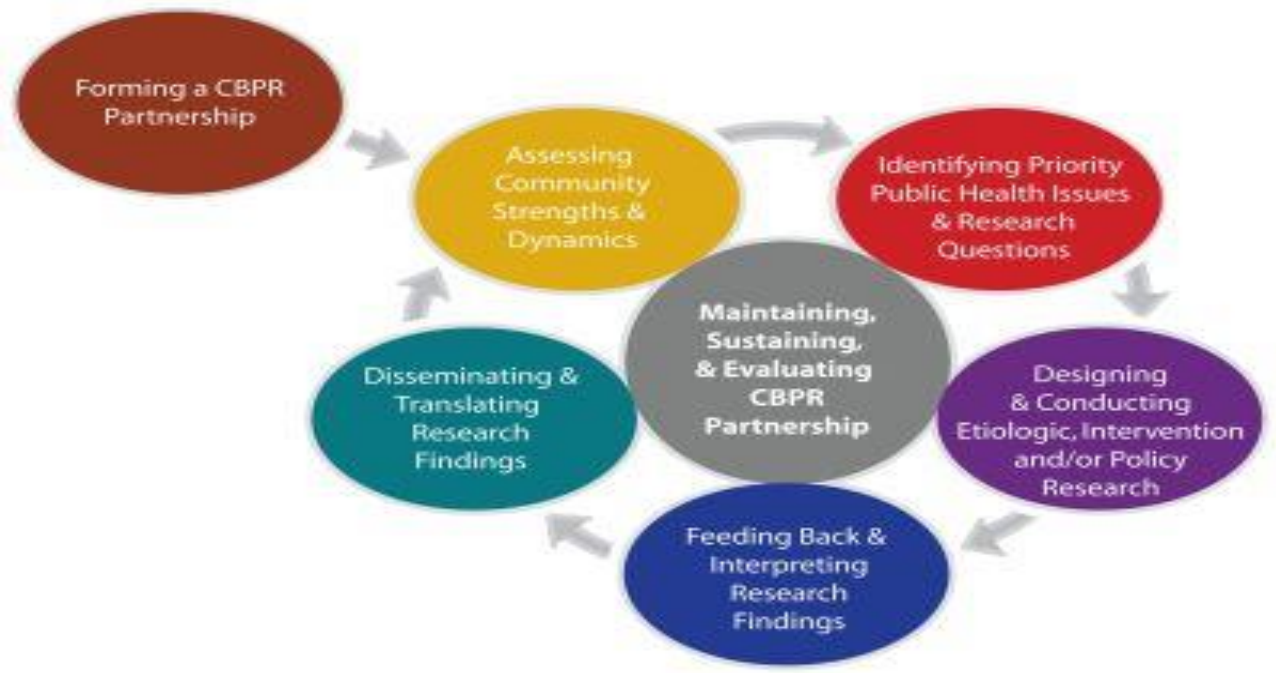
Please refer MHC policies:

- ➢ MHC_RP0119 Emergency Use of a Test Article
- ➢ FDA Guidance "Emergency Use of an Investigational Drug or Biologic"
- ➢ MHC_RP0127 Expanded Access of Investigational Drugs and Devices

COMMUNITY BASED PARTICIPATORY RESEARCH (CBPR)

1. What is CBPR?

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.



2. How IRB review CBPR studies?

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?

- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)

- How will the research outcomes be disseminated to the community?
- Is there a partnership agreement or memorandum of understanding to be signed by the MHC investigator and community partners that describes how they will work together?

3. How can we improve IRB approach towards the CBPR studies?

More effective training in CBPR

Each IRB should have one member fluent in CBPR

Improve communication

COMMUNICATION AND OUTREACH TO CURRENT AND PROSPECTIVE RESEARCH PARTICIPANTS

1. Goals of Participant communication and Outreach Program

MHC Program focuses on:

- ✓ communication
- ✓ education
- ✓ evaluation

MHC provides educational opportunities to:

- ✓ Current and prospective research participants
- ✓ Community members

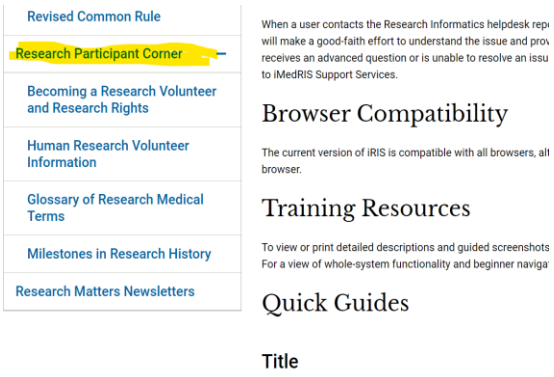
2. Why Research Communication is so important?

- Establish trust
- Convey a meaningful and informative message
- Empowering people in their search for treatment or ways to improve their health
- Understanding your audience
- Understanding the health challenges, they face
- Providing information that is easily accessible and understood.

3. Where can I find Outreach Resources and Educational Materials?

MHC dedicates a section of the research website https://www.mclaren.org/main/iris-research to research participants entitled “Research Participant Corner”. This webpage provides basic information about research to help inform decision-making about participation, a glossary of research terms, FAQs, history, and contact information for Research Integrity and the IRB.

MHC provides links within its Research Participant Corner webpage to information from OHRP and FDA that provide information to the general public about research and research participation.



4. Who manages Outreach Program at MHC?

- Who provides Education?
  Research Compliance QI and Education Specialist

- Who Evaluate the outreach program?
  The Corporate Manager of HRPP at MHC

Please refer to the following MHC policies for further review:
MHC_RP0301 Education and Quality Improvement Program-EQuIP
MHC_RP0202 Annual Evaluations of the Human Research Protection Program