McLaren HEALTH CARE		Policy Title:	Use of Drugs and Biologics in Human Subject Research
Effective Date:	July 20, 2012	**Policy Number:**	MHC_RP0118
Review Date:	August 14, 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. The purpose of this policy is to establish guidelines for the submission and the review of human subjects' research involving the use of an investigational drug, an approved drug used in a manner consistent with the approved product labeling or a biological product.

1.2. This policy is to ensure the use of investigational drugs, biological products, or Food & Drug Administration (FDA) approved drugs are used in a manner consistent with the approved product labeling meet the requirements of McLaren Health Care (MHC), the FDA, and when applicable, Department of Health and Human Services (DHHS) regulations.

2. Scope

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

3. Definitions

3.1. Refer to Appendix I *"Definitions"*

4. Policy

4.1. Sponsors and clinical investigators must comply with the regulations and ensure research conducted involving investigational drugs receives the required review and approval.

4.2. For proposed human subjects research involving an investigational drug or biological product, investigators must ensure the research is conducted under an FDA approved IND or BLA unless the research meets FDA's criteria for an exemption from the IND and BLA regulations.

4.3. Studies involving investigational drugs are subject to the same new and continuing review requirements as for human subjects' research.

4.4. IRB approval must be obtained before the study begins.

4.5. The MHC IRB will ensure all requirements have been met when reviewing and approving research involving investigational drugs.

5. FDA Exemptions

5.1. The following categories of clinical investigations are exempt from the requirements of FDA regulations for IRB review:

5.1.1. 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)].

5.1.2. 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 Food and Drug Administration 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)].

6. Procedure

6.1. The PI must indicate on the IRB application whether the research involves the clinical investigational of a drug or biologic classified as a drug.

6.1.1. If so, the PI must indicate if there is an IND for the research and provide documented assurance from the sponsor that the manufacture and formulation of investigational or unlicensed test articles conform to federal regulations.

6.1.2. If there is an IND, investigators will be asked for evidence of the IND, which could be a:

6.1.2.1. Protocol document with IND.

6.1.2.2. Letter/communication from FDA.

6.1.2.3. Letter/communication from sponsor.

6.1.2.4. Other documents and/or communication verifying the IND.

6.1.3. If the clinical investigation of a drug or biologic is classified as a drug or biologic and there is no IND, the PI must provide a rationale why it is not required.

6.2. During the pre-review process, the IRB Analyst will confirm whether FDA regulations are applicable.

6.2.1. If FDA regulations apply and the research is not exempt, the IRB Analyst will indicate on the agenda that the protocol is an FDA-regulated study.

6.2.2. During the pre-review process, the IRB Analyst will confirm:

6.2.2.1. Whether there is an IND and if so, whether there is appropriate supporting documentation.

6.2.2.2. Whether the IND number is valid by assuring consistency across documents.

6.3. Unless a study meets one of the exemptions below, it is subject to IND regulations. Assigned reviewers will confirm whether the research falls into one of the following categories:

6.3.1. Exemption 1: Exemption for Clinical Investigations involving a Lawfully Marketed Drug(s) 21CFR312.2(b)(1) *and if all* the following requirements are met:

6.3.1.1. The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug.

6.3.1.2. In the case of a prescription drug the research is not intended to support a significant change in the advertising for the product.

6.3.1.3. The research does not involve a route of administration or dosage level, use in a subject population, or other factors that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

6.3.1.4. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

6.3.1.5. The research is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].

6.3.1.6. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].

6.3.2. Exemption 2: For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, an IND is not necessary if:

6.3.2.1. it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

6.3.2.2. it is shipped in compliance with 312.160.

6.3.3. Exemption 3: Exemption for a Clinical Investigation involving a Placebo 21CFR312.2(b)(5)

6.3.3.1. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

Note: Additional requirements apply for research in children/minors based on FDA Subpart D final rule.

6.3.4. Exemption 4: 21 CFR 320.31(b) and (d): Bioavailability or Bioequivalence (BA/BE) studies ***if all*** the following conditions are met:

6.3.4.1. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic.

6.3.4.2. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product.

6.3.4.3. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively], and

6.3.4.4. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].

6.3.5. Exemption 5: 21 CFR 361.1: Research using a radioactive drug or biological product ***if all*** the following conditions are met:

6.3.5.1. It involves basic research not intended for immediate therapeutic, diagnostic, similar purposes, or otherwise to determine the safety and efficacy of the product.

6.3.5.2. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA.

6.3.5.3. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans and

6.3.5.4. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

6.3.6. Exemption 6: FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all the following conditions are met:

6.3.6.1. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry.

6.3.6.2. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject.

6.3.6.3. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies.

6.3.6.4. The quality of the cold isotope meets relevant quality standards, and

6.3.6.5. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts 56 and 50, respectively]

6.4. When applicable, minutes from the meeting will document the subsequent decision regarding whether to approve the study.

6.5. The investigator will be notified in writing of the IRB's determination.

7. Responsibilities:

7.1. Investigator Responsibilities: Ensure that the research does not begin until a valid IND is in effect. This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND. It also includes:

7.1.1. Complying with federal regulations, state and local laws, and all IRB determinations.

7.1.2. Submitting an IRB application describing the proposed research involving an investigational drug.

7.1.3. The PI must obtain approval from the IRB before initiating any research activities.

7.1.4. The PI proposing the drug research will be required to provide a plan – to be evaluated by the IRB - that includes storage, handling, security, dispensing, and documentation of the of drugs or biologics investigated or evaluated in the proposed research study.

7.1.4.1. The PI is responsible for the investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability.

7.1.4.2. All drugs received for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of PI's control. Proper instructions on the use of the drugs must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the drug and the disposition of remaining drugs at the conclusion of the investigation.

7.1.5. The PI shall report all unanticipated problems involving risk to subjects or others (UPIRSO) per Policy *MHC_RP121 "Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)."*

7.1.6. The PI shall report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug (21 CFR 312 (b)) according to the procedures in the protocol.

7.1.7. Submit a final report to the IRB upon completion of the study.

7.1.8. When a PI files an IND or IDE, the PI is considered the sponsor and as such is accountable for all the FDA regulatory responsibilities and reporting obligations of both the PI and the sponsor, as described in the FDA regulations. The PI will be asked if he/she also acts as the sponsor of the research and, if so, will be asked to affirm that he/she has reviewed the **Guidance Document on Requirements of the Sponsor and the Investigator as a Sponsor** and will comply with the regulatory responsibilities of a sponsor.

7.1.9. When the research requires an IND, the PI must not begin the research until a valid IND is in effect. This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND.

7.1.9.1. The IND goes into effect 30 days after the FDA receives the IND unless the sponsor receives earlier notice from the FDA.

7.1.10. *When required by the Sponsor, the PI will maintain the following:*

7.1.10.1. Current curriculum vitae (CV)

7.1.10.2. Protocol

7.1.10.3. Records of receipt and disposition of drugs

7.1.10.4. List of any co-investigators with their curriculum vitae

7.1.10.5. Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation.

And

7.1.10.6. Case histories with documentation on evidence of drug effects. *NOTE:* All unexpected adverse effects are reportable; even if the investigator considers that the event is not related to the drug. All unexpected adverse effects shall be reported immediately to the IRB in the manner defined by the protocol.

7.1.11. The PI will maintain IRB correspondence including, but not limited to, IRB approval letters and IRB approved consent forms.

7.2. Sponsor-Investigator Responsibilities:

7.2.1. Demonstrate and document in the IRB application their knowledge of the additional responsibilities associated with being both the study sponsor (IND or BLA holder) and study investigator.

7.2.1.1. An investigator-sponsor is responsible for all requirements of both the Investigator and the Sponsor and the applicable federal regulations.

7.2.2. Provide the IRB with a copy of the written communication from the FDA documenting the IND/BLA number or exemption from the IND/BLA requirement.

7.2.3. Maintain appropriate storage and handling of investigational drugs and/or biological products used in the research.

7.2.4. Ensure the research does not begin until a valid IND is in effect. This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND.

7.3. IRB Responsibilities:

7.3.1. The IRB will review the research for compliance with MHC policies and procedures, FDA and when applicable, DHHS, regulations.

7.3.2. The IRB will review the research using the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

7.3.3. Verify if the proposed human subject research involves an investigational drug or biological product.

7.3.4. Verify that appropriate documentation of the IND/BLA or exemption is included in the IRB submission.

7.3.5. The IRB will review the control plan and determine whether it is adequate.

7.3.5.1. If the Chair determines that the IRB does not have the necessary expertise to evaluate the plan, outside consultation will be used.

7.3.6. Confirm the investigational drug or biological product has a valid IND/BLA number or meets the criteria for exemption from the requirements per 21 CFR312.2(b) and 21 C FR 32 .31.

7.3.6.1. Assess the adequacy of the PIs (or the investigator-sponsor's) plan for storage and handling of the drug/or biological product.

8. References:

8.1. 21 CFR 50

8.2. 21 CFR 56

8.3. 21 CFR 312

8.4. MHC_RP121 "Reporting Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)"

8.5. Appendix I "Definitions"

8.6. FDA "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Charging for Investigational Products (1998)

9. Previous Revisions: 12/1/12, 3/14/13, 11/21/15, 12/5/21

10. Supersedes Policy: MHC_RP0125 "Use of Drugs and Biologics in Human Subject Research"

11. Approvals:

MHC Institutional Review Board acknowledgment: 7/20/12, 12/4/15, 4/14/16

Signature on File *1/31/23*

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Justin Klamerus, MD, MMM Date
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