Main Line Health, Inc. and Main Line Health Inc. Subsidiaries

Working Together to Serve the Community

This policy applicable to:	**☒All Subsidiaries ☐All Hospitals** **☐All Acute Care Hospitals**	**☐BMRH** **☐Mirmont Treatment Center**

MAIN LINE HOSPITALS, INC.

INSTITUTIONAL REVIEW BOARD

POLICY AND PROCEDURE MANUAL

Reviewed and Revised 2014
Reviewed and Revised 2016
Reviewed and Revised 2018
Reviewed and Revised 2023

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
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The IRB Procedures contained herein provide the IRB and research investigators with the necessary information to comply with the Main Line Hospitals policy and principles relating to investigations involving human subjects. The Procedures contain the framework for the conduct of ethical human research while citing the legal obligations to control its parameters.

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **I**

Subject: **EDUCATION REQUIREMENTS FOR INDIVIDUALS INVOLVED IN HUMAN SUBJECTS RESEARCH ACTIVITIES AT MAIN LINE HOSPITALS**

Main Line Hospitals IRB (MLH IRB) is responsible for providing, through the Office of Research Protections (ORP), an education program on the ethics of conducting human subjects research and the federal regulations pertaining to such research for all personnel involved in the conduct of research studies using human subjects at Bryn Mawr Hospital, Lankenau Medical Center, Paoli Hospital, Riddle Hospital, Bryn Mawr Rehabilitation Hospital, and other sites under the jurisdiction of the MLH IRB.

Training requirements described in this policy apply to all investigators and staff engaged in research reviewed by the MLH IRB or a designated external IRB. The MLH IRB requires all individuals responsible in the design, conduct, and reporting of a study to complete and remain current with the training requirements before approval is granted. This includes, but is not limited to, investigators, sub-investigators, staff, coordinators and nurses involved in the conduct of a study. This policy also applies to all MLH IRB administrative staff and all MLH IRB members. Each person covered by this policy must successfully complete the education program and remain current with the training requirements as described below.

PROCEDURES

Computer Based Training and Continuing Education:

The ORP uses a subscription online service to provide and monitor the training requirement for human subjects research investigators, research support staff, MLH IRB members, and MLH IRB Administrative staff. The program is sponsored by the Collaborative Institutional Training Initiative (CITI). Completion of the appropriate curriculum is required to conduct or be involved in human subjects research. Investigators and their research support staff, MLH IRB administrative staff, and MLH IRB members are required to remain current with all training requirements.

The Education Program for individuals involved in Human Subjects Research at MLH consists of the categories listed below.

1. Research Personnel including Investigators and Staff:

A. Human Subjects Training - The CITI online training program consisting of modules and groups in human subjects research that must be completed by all current and new investigators and their research support staff. The training groups vary based on the type of research that is conducted. (See TRAINING

section below) Successful completion of the curriculum is required. Recertification of the training must be completed every three (3) years[1].

B. Good Clinical Practices (GCP) - The CITI training program on GCP that must be completed by NIH-funded research investigators and their research support staff. GCP is usually required on behalf of industry sponsored/funded research as a sponsor requirement and not on behalf of the MLH IRB. Successful completion of the curriculum is required Recertification of the training must be completed every three (3) years.

C. Conflict of Interest (COI) - The CITI training program on COI must be completed by research investigators and their research support staff. Refer to the *MLH IRB Policy III Conflicts of Interests: Researchers and Research Staff* for more information on the MLH IRB requirements for COI training. Successful completion of the curriculum is required. Recertification of the training must be completed every four (4) years and as required in the *MLH IRB Policy III on Conflicts of Interests: Researchers and Research Staff*.

2. IRB Members and IRB Administrative Staff:

A. MLH IRB Members and MLH IRB Administrative Staff - The CITI training for MLH IRB Members and MLH IRB Administrative Staff. Recertification of the training must be completed every three (3) years.

TRAINING REQUIRMENTS

The link to the online CITI Training course is available on the ORP website at https://www.mainlinehealth.org/research/office-of-research-protections/policies-procedures or directly at www.citiprogram.org. There are several groups to choose from as outlined below. ***Research personnel may meet the criteria of more than one group, depending on the research that is conducted.***

Group 1 - Biomedical Research: For research personnel who engage in Biomedical research. Recertification of the training must be completed every three (3) years[1].

Group 2 - Social and Behavioral Research: For research personnel who engage in Social and Behavioral research that does not involve biomedical procedures. This type of research typically involves questionnaires, interviews, focus groups, direct or participant observation, and may include certain types of non-invasive specimen collection. This group does **NOT** satisfy the educational requirements for Biomedical Research. ***Research personnel who engage in biomedical research must also complete the Group 1 Module***. Recertification of the training must be completed every three (3) years[1].

Group 3 - Data or Specimen ONLY Research: For research personnel who engage exclusively in secondary data analysis of data, human tissues and/or samples. This group does **NOT** satisfy the educational requirements for Biomedical or Social and Behavioral Research. If you are planning to conduct Biomedical or Social and Behavioral research, you are required to take Group 1 and/or Group 2.

[1] Two refresher courses, three years apart are permitted prior to re-taking the original course.

Group 4 – MLH IRB Members and MLH Administrative staff. This group does **NOT** satisfy the educational requirements for Groups 1, 2, or 3. Recertification of the training must be completed every three (3) years.

Group 5 – Good Clinical Practices (GCP). For research personnel who engage in NIH-Funded Research or may be required by sponsors of industry-funded research. This group does **NOT** satisfy the educational requirements for Groups 1, 2, 3, or 4. Recertification of the training must be completed every three (3) years**.**

Group 6 – Exempt Research. For research personnel who engage in Exempt research. Recertification of the training must be completed every three (3) years**.** This group does **NOT** satisfy the educational requirements for Groups 1-5. **Note:** Groups 1-3 will satisfy the training requirements of Group 6.

Conflict of Interest – For ALL research personnel. Recertification of the training must be completed every **four** (4) years and as required in the *MLH IRB Policy III on Conflicts of Interests: Researchers and Research Staff*. Refer to the policy for more information on the IRB requirements for conflict of interest training.

Monitoring:

The training status of the Principal Investigator(s) (PI) will be checked by the ORP staff upon receipt of new study and continuing review submissions. If training requirements are not satisfied for the PI(s) of a new study, the study approval will be held until all training requirements are met. If the training requirements are not satisfied by the PI(s) when a continuing review submission is made, the ORP will make up to three (3) attempts to request completion of the training. If training requirements are not satisfied within one (1) week of the final request, the individual(s) will be removed from the study(s) and will be contacted by the Director of the ORP to address the outstanding training.

PI Responsibilities for training oversight:
Principal Investigators (PI), or their documented designee, are responsible to ensure that all investigators and research staff named to the protocol have received the appropriate CITI training and their training remains current without expiration for the duration of the IRB approved protocol lifespan.

The PI(s), or their documented designee, will ensure that the retention of electronic or paper documentation as evidence of completion of required CITI training, and follow applicable policies regarding the frequency records are periodically checked. The PI(s) are responsible for ensuring that all research personnel named to the protocol have completed and retain current CITI certification for the lifespan of the IRB approved protocol. The ORP may periodically confirm that training and research records are current and maintained in good order during ORP quality assurance (QA) evaluations of MLH protocols.

Origination Date: 12/2003
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. II

Subject: OVERVIEW OF THE INSTITUTIONAL REVIEW BOARD

IRB STRUCTURE

The Board of Trustees of Main Line Hospitals, Inc. has approved the establishment of an Institutional Review Board (Main Line Hospitals IRB (MLH IRB), under a Federal-Wide Assurance (FWA) with the Office for Human Research Protections (OHRP), Division of the Department of Health and Human Services (DHHS). Entities included under the FWA are Main Line Hospitals, Inc., which includes Lankenau Medical Center, Bryn Mawr Hospital, Bryn Mawr Rehabilitation Hospital and Paoli Hospital, Riddle Hospital, Mirmont Treatment Center and the Lankenau Institute for Medical Research (LIMR). The Institution has one MLH IRB to provide oversight and approval of research conducted at any site included under the FWA or within the Main Line Health System.

The Chair and the Vice-Chair(s) of the MLH IRB will be appointed by the Main Line Hospitals Board of Trustees through the Institutional Official (IO). The Vice-Chair(s) shall assume the duties of the MLH IRB Chair, in the IRB Chair's absence or at the MLH IRB Chair's discretion.

Refer to Administrative Policy IRB: Compliance, Federal Regulations Governing the Protection of Human Research Subjects for additional information on the authority of the IRB.

IRB MEMBERSHIP

The Main Line Hospitals Board of Trustees appoints the MLH IRB Chair and members of the MLH IRB. The names and Curriculum Vitis of the appointees, alternates and regular members, are submitted for approval to the Quality, Safety and Equity Committee (QSEC) of the MLH Board by the Main Line Hospitals IO for the MLH IRB through the Office of Research Protections (ORP) Director.

In nominating MLH IRB members for appointment, the IO and/or ORP Director will ensure all the following conditions are met for the MLH IRB:

- The MLH IRB will consist of at least five (5) members.
- MLH IRB members will have professional competence and varying backgrounds, experience and expertise as necessary to promote complete and adequate review of research activities commonly conducted by the organization.
- The MLH IRB will be sufficiently qualified through the experience, expertise, and diversity of its members, including considerations of race, gender, cultural backgrounds, and sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the

rights and welfare of human subjects

- The MLH IRB will include persons knowledgeable about institutional commitments and regulations, applicable laws, and standards of professional conduct and practices
- If the MLH IRB regularly reviews research that involves a vulnerable category of subjects such as children, pregnant women, human fetuses and neonates mentally disabled persons, or economically or educationally disadvantaged persons, the IO will nominate one or more individuals who are knowledgeable about and experienced in working with these subjects. When the MLH IRB reviews research involving prisoners, a prisoner representative must be present. Refer to MLH IRB Policy on *Research Involving Prisoners as Subjects* (XXVI) for information on MLH IRB requirements for prisoners.
- The MLH IRB will not consist entirely of members who are all males or all females.
- The MLH IRB will not consist entirely of members of one profession.
- The MLH IRB will include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- The MLH IRB will include at least one member who is not otherwise affiliated with organization and who is not part of the immediate family of a person affiliated with the organization.
- The MLH IRB will include at least one member who represents the perspective of research subjects (e.g., non-affiliated member)
- There is no limitation on the length of service that any MLH IRB member may serve.
- No individual responsible for Main Line Health, Main Line Hospitals, or other MLH Affiliate business development, including those with responsibilities for grants, contracting, raising funds, garnering support for research, and business development may be appointed as an MLH IRB member or be involved in the daily operation of the review process.

The MLH IRB may invite individuals with competence in special areas to assist in the review of protocols that require expertise beyond or in addition to that available on the MLH IRB. These individuals, consultants, may not vote with the MLH IRB.

Other individuals also attend convened meetings as necessary. These individuals advise the MLH IRB on the acceptability of proposed research in terms of regulatory requirements, institutional commitments, applicable laws, and standards of professional practices and conduct, e.g., MLH Chief Compliance Officer.

MLH IRB members including alternates, receive human subjects protections education related to federal regulations and guidance, Human Research Protection Program policies and procedures, and IRB review processes. Minimally, initial training in human subjects protection, with continuing education every three years is required (e.g., completion of Collaborative Institutional Training Initiative (CITI) modules). MLH IRB members also receive additional education/new information at meetings and via email announcements.

Member qualifications are reviewed as needed and no less than once every two (2) years. A current membership roster is maintained by ORP and the FWA is updated as required.

No member may participate in the MLH IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the MLH IRB.

IRB MEETINGS
There is one (1) scheduled MLH IRB meeting a month. Additional meetings may be scheduled as needed.

QUORUM
ORP staff attending MLH IRB meetings are responsible for determining that meetings are appropriately convened before the discussion and vote for each review. For convened MLH IRB Meetings, a quorum is defined as follows:

- The majority, i.e., more than half, of the MLH IRB full/voting members listed on the membership roster are present.
- At least one member is present whose primary concerns are in nonscientific areas.
- At least one member is present whose primary concerns are in scientific areas.
- For Food and Drug Administration (FDA) regulated research, a member is present who is a licensed physician.
- Attendance of an unaffiliated member at least 9 of 12 meetings per year.
- Attendance of at least one member who represents the perspective of research subjects, e.g., non-affiliated member, at least 9 of 12 meetings per year.
- When the MLH IRB regularly reviews a vulnerable category of research such as children, pregnant women human fetuses and neonates, or handicapped or mentally disabled persons, a member is present representing population's interests, and their vote will count towards quorum.

When the MLH IRB reviews research involving prisoners, the prisoner representative is present.

If both an MLH IRB full/voting member and his/her respective alternate(s) are present, only one may vote and be counted toward quorum.

Comments from members unable to attend a meeting that have been provided the meeting materials for discussion in advance, e.g., by fax or e-mail, may be considered for discussion by the attending MLH IRB members however the member unable to attend may not be counted as votes or toward the quorum for convened meetings.

Any member may participate by teleconference or videoconference, provided he/she has received all materials before the meeting and can actively and equally participate in the discussion.

If quorum is not met, then MLH IRB voting cannot take place and the items on the agenda will be tabled/deferred until the next convened IRB meeting.

If quorum is lost during a convened meeting. e.g., due to a member leaving the meeting, then no further voting can take place until quorum is restored and the remaining items on the agenda will be tabled/deferred until quorum is restored or the next convened MLH IRB meeting.

ORP staff attending MLH IRB meetings are responsible for recording the attendance of members as they enter and leave the room. If quorum is lost, ORP staff will notify the IRB Chair or Vice-Chair that no further actions can be taken until/unless quorum is restored.

ALTERNATES

- Federal regulations allow organizations to appoint an alternate(s) to substitute for an MLH IRB full/voting member(s) who is unable to attend so that MLH IRB business may move forward in a timely manner. Alternates are appointed by the same

process and for the same length of time as MLH IRB full/voting members.

- IRB alternates function as regular board members when they are in attendance. An alternate may substitute for the primary MLH IRB member for an entire meeting or at any time during a meeting.
- Each alternate member is paired with one or more regular members with comparable experience and expertise, as possible. The MLH IRB roster identifies the primary member(s) for whom each alternate may substitute. Minimally, alternates and members are paired by scientific "class," as physician scientists, when applicable, other scientists, and non-scientists. The MLH IRB roster will identify the member(s) for whom each alternate can substitute.
- When an alternate substitutes for a regular MLH IRB member, the alternate receives and reviews the same materials that the regular member received, or would have received, and MLH IRB minutes document that an alternate replaced a regular member.

IRB MEMBERSHIP ROLES AND RESPONSIBILITIES

1. MLH IRB Chair

The MLH IRB Chair is selected based on experience and expertise and previous familiarity with an IRB. The MLH IRB Chair is a voting member and has primary responsibility for the following:

- Providing leadership to the MLH IRB to help ensure the rights and welfare of human subjects participating in research reviewed by the MLH IRB
- Conducting convened meetings and reviewing and approving the minutes documenting MLH IRB discussions and findings
- Communicating with investigators and/or administrators to resolve controversial and/or procedural matters relating to research approval and conduct.
- Annually completing Conflict of Interest Disclosure Form and disclosing any potential conflicts prior to MLH IRB review of the research for which a conflict may exist.
- Managing conflicts of interest by ensuring that IRB members with conflicts are not present for review of research for which a conflict may exist.
- Maintaining confidentiality of MLH IRB-related information
- Administering Board decisions and maintaining the independence of the IRB
- Signing correspondence communicating and documenting IRB decisions
- Reviewing and approving research by expedited and exempt procedures with the ORP Director or designee
- Making research determinations with the ORP Director or designee. Refer to the MLH IRB Policy on Research Determination and Activities Requiring IRB Review (V)
- Participating in the development of meeting agendas, policies, procedures, and educational efforts to support the human research protection program.
- Maintaining a current knowledge of and assuring compliance with relevant regulations, laws, and policies related to the protection of human subjects.
- Remaining current with IRB training requirements (CITI)
- Regularly consulting with the ORP Director and ORP staff regarding MLH IRB issues
- Assisting with investigations and review of alleged noncompliance with human subjects protections requirements as required in the MLH IRB Policy on Noncompliance (XX)
- Assisting with institutional efforts to promote a culture of shared responsibility for the safety and welfare of research subjects.

2. Vice Chair(s)

The Vice Chair(s) support the role and responsibilities of the MLH IRB Chair. The Vice

Chair(s) attend MLH IRB meetings and chair convened meetings when required. The Vice Chairs assume duties as delegated by the Chair. In addition, the Vice Chair(s) are voting members and responsibilities include all the following:

- Annually completing the Conflict of Interest Disclosure Form and disclosing any potential conflicts prior to MLH IRB review of the research for which a conflict may exist.
- Maintaining a current knowledge of and assuring compliance with relevant regulations, laws, and policies related to the protection of human subjects.
- Remaining current with MLH IRB training requirements, CITI.
- Maintaining confidentiality of MLH IRB related information
- Reviewing and approving research by expedited procedures, when designated by the MLH IRB Chair to perform this review.

3. MLH IRB Members

MLH IRB member responsibilities include all of the following:

- Attending IRB meetings and actively participating in the review of research, unless arrangements have been made for the alternate's attendance.
- Completing initial training in human subjects protection for MLH IRB members prior to voting on any research and remaining current with MLH IRB training requirements.
- Understanding and applying the principles of the Belmont Report and the federal regulations related to the protection of human subjects.
- Providing timely written comments on research undergoing MLH IRB review, when required
- Annually completing the Conflict of Interest Disclosure Form and disclosing any potential conflicts prior to MLH IRB review of the research for which a conflict may exist.
- Maintaining confidentiality of MLH IRB related information
- Timely declaration of potential conflicts of interests at convened meetings
- Reviewing and approving research by expedited procedures, when designated by the MLH IRB Chair to perform this review.

MEMBERSHIP ROSTER

Official Roster for the MLH IRB contains the following information for each full/voting member and alternate:

- Name
- Earned degree(s)
- Representative Capacity
- Scientist status (scientist or non-scientist)
- Affiliation Status
- Experience
- Employment or other relationship with the Institution
- Primary members for whom alternate members may substitute.

VOTING

Each member present is entitled to one vote. In the absence of a primary member, the alternate member who is substituting votes. The Committee decision is by a majority vote. Other individuals having special expertise relevant to a particular matter, who may be invited to attend specific meetings to assist in the review, may not vote.

REVIEW OF IRB COMPOSITION AND PERFORMANCE

The composition of the Committee is reviewed at least annually by the ORP Director and the

MLH IRB Chair to determine if adjustment of the membership or composition is necessary to meet regulatory and organizational requirements.

The MLH IRB Chair and ORP Director, with input from ORP staff, evaluate individual MLH IRB member performance in terms of attendance, knowledge, and overall review quality no less than once every two years. Feedback, face-to-face or in writing, is provided to MLH IRB members by the MLH IRB Chair and/or ORP Director. Feedback may be provided to supervisory authorities as required.

The IO and ORP Director, with input from MLH IRB members and ORP staff as necessary, evaluate the MLH IRB Chair's and Vice Chair's performance and provide feedback no less than once every two years. The IO is responsible for addressing performance issues with the MLH IRB Chair and Vice Chair(s) and for nominating a new Chair and Vice Chair(s) when necessary. Feedback, face-to-face or in writing, is provided by the IO. Feedback may be provided to supervisory authorities as required.

ORP staff will update the roster with OHRP when changes in IRB membership are approved.

MINUTES

ORP staff follow "SOP 103: Preparation and Review of IRB Minutes" to prepare and process meeting minutes.

Minutes are recorded by ORP to show the following:

- attendance noting all participants present, absent from and returning to meeting, and when alternate member replaces a primary member.
- Initial and continued presence of a majority of members, i.e., quorum, including at least one non-scientist.
- acknowledgement the Chair requested members to disclose any conflicts of interest.
- acknowledgement the Chair confirmed members in attendance have received and have access to the meeting agenda and review materials.
- description of educational or training materials presented.
- that a licensed physician was present for review of all FDA protocols
- separate deliberations for each item
- actions taken by the MLH IRB
- the vote on MLH IRB actions including the number of members voting for, against, and abstaining.
- the level of risk determined by the IRB.
- the basis for requiring changes in or disapproving research.
- deferrals
- a written summary of the discussion of controverted issues and their resolution
- information provided by a consultant.
- the names of MLH IRB members who leave the meeting because of a conflicting interest, noting that conflict of interest is the reason for absence.
- for initial and continuing review, the approval period and the frequency of continuing review
- required determinations and protocol-specific findings justifying determinations for:
    - waiver or alteration of the consent process
    - waiver or alteration of HIPAA Authorization
    - research involving pregnant women, fetuses, and neonates.
    - research involving prisoners.
    - research involving children.
    - research involving subjects with diminished capacity to consent.
    - significant/non-significant risk device determinations

All Minutes of the MLH IRB are approved by the convened MLH IRB during the subsequent meeting and are maintained by ORP in an electronic format in a secured share drive. Minutes of the MLH IRB are available to the IO.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **III**

Subject: **CONFLICTS OF INTEREST: RESEARCHERS AND RESEARCH STAFF**

POLICY

Main Line Hospitals Institutional Review Board (MLH IRB) promotes objectivity in research by ensuring investigator's and research staff's financial conflicts of interest or even the appearance of conflicts of interest are managed, minimized or eliminated when appropriate. The MLH IRB ensures an existing financial conflict of interest does not adversely affect the protection of subjects or the integrity of the research.

SCOPE

The policy applies to all investigators and research staff conducting research under the jurisdiction of the MLH IRB. In addition to the requirements outlined in this policy, human subjects research that is sponsored by the Department of Health and Human Services (DHHS) must comply with the Lankenau Institute for Medical Research (LIMR) Financial Conflict of Interest Policy for Public Health Services funded research. Institutional conflicts of interest are not addressed in this policy.

DEFINITIONS

1. **Investigators and Research Staff:** Includes those individuals involved in the design, conduct or reporting of human subjects research and their *immediate family members*[2]. This includes but is not limited to the investigators, subinvestigators, study coordinators, staff, nurses and any others involved in the conduct of a research study.
2. **Financial Conflict of Interest (FCOI):** Means any Significant Financial Interests that could directly and significantly affect the design, conduct, or reporting of research.
3. **Financial Interest:** Means anything of monetary value, whether or not the value is readily ascertainable.
4. **Financial Interests which must be disclosed:** Means any personal, professional, financial or ownership interest or other beneficial interest in the research, sponsor, product or service being tested or held by the investigators or research staff including immediate family and may include any of the following interests:
    a. Ownership or interest of any value including but not limited to stocks and options, exclusive of interests in a publicly traded, diversified mutual fund.
    b. Compensation of any value including but not limited to salary, honoraria, paid authorship, consultant fees, royalties, equity or other income.

[2] "Immediate family member" means: spouse and dependent children

c. Proprietary interest of any value including but not limited to patents, trademarks, copyrights, licensing agreements or other intellectual property rights and interests.
d. Per subject or other recruitment bonuses paid in addition to the negotiated research budget.
e. A financial interest or compensation of any value which will be affected by the outcome of the research.
f. Serves or has ever served as a board member, executive, employee, consultant, advisor or speaker.
g. Any other interest or potential interest that may conflict with his/her duties in the research and may affect a subject's voluntary and informed choice to participate in the research.

5. **Significant Financial Interest (SFI) means:** A financial interest consisting of one or more of the following that reasonably appears to be related to a specific research study:
   a. With regard to any publicly traded entity, a SFI exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure and the value of any equity interest in the entity as of the date of disclosure, when aggregated for the preceding 12 months and immediate family members, exceeds $10,000. For purposes of this definition, remuneration includes salary and any payment for services not otherwise identified as salary, e.g., consulting fees, honoraria, paid authorship; equity interest includes any stock, stock option, or other ownership interest as determined through reference to public process or other reasonable measures of fair market value.
   b. With regard to any non-publicly traded entity, a SFI exists if the value of any remuneration received from the entity in the twelve months preceding the disclosure, when aggregated for the preceding 12 months and immediate family members exceeds $10,000.
   c. With regard to any non-publicly traded entity, a SFI exists when any equity interest (e.g., stock, stock option, or other ownership interest) is held or
   d. Intellectual property rights and interests, e.g., patents, copyrights, upon receipt of income related to such rights and interests.

PROCEDURE

A. Disclosure: Conflict of Interest Disclosure Forms are submitted to the Office of Research Protections (ORP):
   a. at the time of submission of a new human subjects research protocol investigator and research staff are required to complete a Conflict of Interest Disclosure Form.
   b. with an active human subjects research protocol investigator and research staff are required to complete a Conflict of Interest Disclosure Form at least annually at time of Continuing Review or Annual Update submission.
   c. with an active human subjects research protocol investigator and research staff must update new significant financial interests within 30 days of changes in financial circumstances, i.e., acquisition or discovery, by providing an updated Conflict of Interest Disclosure Form.

B. Training: Investigators and research staff will receive training related to financial conflict of interest at least every four years through the Collaborative Institutional Training Initiative (CITI). Training will be required immediately when:
   a. Financial conflict of interest policies is revised in a manner that changes investigator or researcher staff requirements.

b. An investigator is new to the organization.
c. An investigator or researcher staff member is non-compliant with financial conflict of interest policies and procedures.

C. <u>Evaluation and Management of Financial Conflicts of Interest</u>: ORP will review each Conflict of Interest Disclosure Form received and identify any investigator or research staff who makes a disclosure on the Conflict of Interest Disclosure Form. The Chair of the MLH IRB and ORP Director will evaluate those forms that contain a disclosure and may require action when necessary, such as disclosure in the informed consent. If the IRB Chair or the ORP Director declares a conflict, Conflict of Interest Disclosure Form will be referred to the Main Line Hospitals Designated Institutional Official (IO) for evaluation.

When an SFI appears to be an FCOI or any other interest and has the potential to adversely affect the protection of subjects in terms of the criteria for IRB approval or will adversely affect the integrity of the research, it will be initially be referred to the Research COI (RCOI) Subcommittee for further evaluation. If the RCOI Subcommittee determines that an individual with a Financial Interest has a Financial Conflict of Interest, it will submit its findings and recommendations to the COI Committee of Main Line Health for further deliberation.

When an FCOI has the potential to adversely affect the protection of subjects in terms of the criteria for IRB approval or will adversely affect the integrity of the research an FCOI management plan is required. Management plans may include without limitation removing the affected persons from directly engaging in aspects of the trial that could be influenced inappropriately by the FCOI including, but not limited to, obtaining informed consent, monitoring of study, design of the study, oversight responsibilities, partial or complete divestment.

In addition, a determination shall be made whether the research study may be reviewed by the MLH IRB and whether the study may be conducted at Main Line Health.

Disclosures alone may not be sufficient, and the IRB will make the final determination of what is required to assure subjects are protected and fully informed.

FCOIs are evaluated and management plans are developed prior to IRB review.

IRB PROCEDURES

FCOI management plans developed by the MLH COI Committee are provided to ORP and presented to the MLH IRB at the time of protocol review or during the course of the study as required. The MLH IRB has the final authority to determine whether the research may be approved.

The MLH IRB and ORP are responsible for implementing and monitoring the FCOI management plan. Investigators and research staff will be required to submit an annual report describing compliance with their FCOI Management Plan. Annual reports will be reviewed by the IRB Chair and ORP Director. Deviations from the FCOI Management Plan may be handled under the MLH IRB Policy on Noncompliance (XX).

RECORD KEEPING

Conflict of Interest Disclosure Forms, FCOI Management Plans related to human subjects research, and related documents will be maintained in ORP. Records will be maintained for a

minimum of three years after completion of the research (refer to the MLH Administrative Policy I.96 on Records Management (Retention and Destruction).

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. IV

Subject: CONFLICTS OF INTEREST: IRB MEMBERS[3] AND CONSULTANTS

POLICY

Main Line Hospitals Institutional Review Board (IRB) promotes objectivity in research by ensuring IRB Members, and consultants who are participating in the review of a research study are free of actual or perceived conflicts of interest.

No regular or alternate IRB member or consultant, or their immediate family member, may participate in any type of review (including unanticipated problems and noncompliance) of research in which the member has a conflict of interest, except to provide information as requested.

Due to institutional conflict of interest, no individual responsible for Main Line Health, Main Line Hospitals, or other MLH Affiliate business development, including those with responsibilities for grants, contracting, raising funds, garnering support for research, and business development may be appointed as an IRB member or be involved in the daily operation of the review process.

DEFINITIONS

A conflicting interest of an IRB member, IRB consultant or their immediate family member[4] includes the following:

1. Is a member of the research team.
2. Has a financial interest in the research with a value that cannot be readily determined;
3. Has received or will receive compensation with a value that may be affected by the outcome of the study.
4. Has proprietary interest in research, such as a patent, trademark, copyright, or licensing agreement or royalties from such rights.
5. Has any financial interest in the research.
6. Has received any payments from the sponsor of the research.
7. Is an executive or director of the agency or company sponsoring the research.
8. Has an interest that the IRB member believes conflicts with his or her ability to objectively review a protocol.
9. Has a close personal or professional association with a member of the research team.

A financial interest means anything of monetary value, whether or not the value is readily ascertainable. The financial interests that are considered conflicting interests for IRB members and consultants are the same as those for researchers and research staff.

3 "IRB Members" include all IRB voting and, the Main Line Hospitals, Inc. Designated Institutional Official.

4 "Immediate family member" means spouse and dependent children.

PROCEDURE
These procedures cover those research protocols reviewed at a convened IRB meeting and reviewed using expedited procedure and include the review of unanticipated problems involving risk to subjects or others, review of noncompliance with the regulations or the requirements of the IRB and any other ad hoc reviews requested by the IRB.

A. IRB Members
IRB members are required to complete a Conflict of Interest Form annually.

1. Review by Convened IRB:
a. IRB members should review the list of protocols for an upcoming meeting and should disclose a conflicting interest as soon as possible to the Office of Research Protections (ORP) Staff, ORP Director or the IRB Chair.
b. An IRB member with a conflicting interest on a protocol should not accept the protocol for review and should return it to ORP for reassignment to another reviewer.
c. If an IRB member recognizes a conflicting interest at the IRB meeting, the IRB member must inform the IRB Chair of the conflicting interest.
d. If other IRB members need to request information about the protocol from the IRB member with the conflicting interest, the IRB member may remain in the room during the presentation of the protocol but must then leave the room before the final discussion and vote.
e. The ORP Staff will record in the minutes the name of the IRB member as being absent based on a conflicting interest. The IRB member will not be counted as part of the quorum for the protocol. If quorum is not maintained, no further action may be taken by the IRB on the protocol.

2. Review by Expedited Procedure:
a. IRB members should review the assigned item for review and should disclose a conflicting interest as soon as possible to the ORP Staff, ORP Director or the IRB Chair.
b. An IRB member with a conflicting interest with a protocol should not accept the item for review and should return it to ORP for reassignment to another reviewer.

B. IRB Consultants
1. Prior to engaging a consultant for review of a research protocol, the ORP Staff, ORP Director or the IRB Chair will make an initial assessment whether there is a conflict of interest on the part of an IRB consultant.
2. When requesting a consultant to review a protocol, the ORP Staff will provide the consultant with the IRB Member and Consultant COI Policy in addition to the relevant materials for review and ask if the consultant has a potential conflict of interest with the protocol, as defined in this policy.
3. The IRB cannot use the services of a consultant in the review of a research protocol, in which the consultant has a conflict of interest, as defined in this policy.
4. The ORP will reassign any protocol with which a consultant has a conflict of interest.

DOCUMENTATION
All COI and related documents will be maintained in ORP.

REGULATORY REFERENCES
FDA Regulations: 21 CFR 56.107(e)
DHHS Regulations 45 CFR 46 Protection of Human Subjects 46.107(e)

Origination Date: 05/29/08
Revision Date: 12/20/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. V.

Subject: RESEARCH DETERMINATION AND ACTIVITIES REQUIRING IRB REVIEW

POLICY

Research involving human subjects requires the review of an Institutional Review Board for any research or clinical investigation that involves human subjects as defined below. Research that does not meet the regulatory definition of human research or clinical investigations does not require IRB approval.

DEFINITIONS

1. Research and Related Terms:

a. **Research -** Department of Health and Human Services (DHHS) Regulations - "a systematic investigation, including research, development, testing and evaluation designed to develop or contribute to generalizable knowledge."

i. Systematic investigation - A study following a methodical plan to establish factual information concerning the truth of a specific hypothesis or theory.

ii. Generalizable knowledge - Knowledge that may be justifiably transferred or extrapolated to a broader population or situation than that in which it has been derived

b. **Clinical Trial -** DHHS Regulations – "clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes."

c. **Clinical Investigation -** Food and Drug Administration (FDA) Regulations – a clinical investigation means "any experiment that involves test article(s) and one or more human subjects."

i. Test article - Any drug (including a biological product for human use, medical device for human use), human food additive, color, adaptive, electronic product, or any other article subject to regulation under the jurisdiction of the FDA.

2. Human subject:

a. DHHS Regulations - "A living individual about whom an investigator, whether professional or student, conducting research (1) obtains information or biospecimens through intervention or interaction with the individual and uses, studies or analyzes the information or biospecimens or (2) obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens."

i. *intervention* includes both physical procedures by which information or biospecimens are gathered, e.g., venipuncture, and manipulations of the

subject or the subject's environment that are performed for research purposes.

i. interaction includes communication or interpersonal contact between investigator and subject.
ii. *private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public, *e.g.,* a medical record.
iii. *identifiable private information* is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.
iv. *identifiable biospecimen* is a biospecimen for which the identity of the subject is or may be readily ascertained by the investigator or associated with the biospecimen.

b. FDA Regulations - "An individual who is or becomes a participant in research either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient."

3. Research involving human subjects[5]:

a. DHHS Regulations - Meets the definition of research involving human subjects as referenced in Sections 1 and 2 above.

b. FDA Regulations - Meets the FDA definition of clinical investigation involving human subjects as referenced in Sections 1 and 2 above.

PROCEDURE

Any individual who is unsure whether or not a proposed activity should be classified as research should contact the IRB for guidance with a written description of the project. Investigators have the option to obtain from the IRB documentation that the activity is not subject to IRB review. To obtain documentation, investigators must submit a description of the proposed activity in writing. The IRB Chair or Office of Research Protections (ORP) Director or their designees make the determination.

A. Activities which require IRB review include, but are not limited to:

1. Any experiment that involves a test article and one or more human subjects, that are regulated by the FDA or support applications for research or marketing permits for products regulated by the FDA. Products regulated include foods, including dietary supplements, medical devices, drugs, biological products human food additives, colors, adaptive and electronic products.

2. Collection and use of data about a series of standard procedures or treatments for dissemination or generalization if the activity meets the definition of research involving human subjects.

3. Patient care or the assignment of normal subjects to any intervention that is altered

[5] Although not meeting the regulatory definition of research involving human subjects, the privacy rights of non-living individuals are protected under the Privacy Rule. Review by the MLH IRB, acting as the Privacy Board for research may be required. Refer to Administrative Policy VII 17 on *HIPAA: Use of Protected Health Information for Research* for more information.

for research purposes in any way.

4. A diagnostic procedure for research purposes that is added to a standard treatment.

5. Systematic investigations of innovations in diagnostic, therapeutic procedure or instructional method in multiple subjects in order to compare standard procedure. The investigation is designed to test a hypothesis, permit conclusions to be drawn, thus, to develop or contribute to generalizable knowledge.

6. Emergency Use of an Investigational Test Article. One time emergency use of an investigational test article may proceed without ***prospective*** IRB review and approval. The patients receiving an investigational test article in an emergency setting are generally not considered research subjects and data obtained from patients may not be classified as human research and may not be included in any report of research activities subject to DHHS regulations. **NOTE: The investigator has additional responsibilities, including notifying the IRB, before and/or after the emergency use of an investigational test article. Refer to Policy VIII Emergency Use of an Investigational Test Article for more information**

7. Emergency Medicine Research. Prospectively planned emergency medicine research with investigational drugs, devices, or biologics requires IRB approval. If the investigator intends to request a waiver of the requirement for informed consent, additional requirements must be met including community consultation and public disclosure.

8. In Vitro Device (IVD) Studies. Current FDA guidance indicates that IRB review is required for any IVD study involving human specimens/samples, even when the specimens are leftover human specimens, the research involves no identifiers or the biological materials cannot be linked to any identifying information. FDA regulations do not contain exceptions from the requirements of informed consent on the grounds that the specimens are not identifiable and or that they are remnants of human specimens collected for routine clinical care or analysis that would otherwise have been discarded. Nor do FDA regulations allow IRBs to decide whether or not to waive informed consent for research involving leftover or unidentifiable specimens.

   PLEASE NOTE: Subsequent to FDA issuing the guidance previously noted, FDA further clarified that; "…(FDA)…does not intend to object to the use, without informed consent, of leftover human specimens in investigations that meet the criteria for exemption from the Investigational Device Exemptions regulation at 21 CFR 812.2(c)(3), as long as subject privacy is protected by using only specimens that are not individually identifiable." Please contact ORP Director or IRB Chair for further clarification.

9. See 2006 FDA *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*.

10. Individually Identifiable Data and Human Tissue. Use of data or human tissue for research which is identifiable requires IRB review.

11. Investigator Initiated Research. An investigator who both initiates and conducts,

alone or with others, a human research project or clinical trial regardless of source of funding or support.

12. Resident/Fellow Research. Directed or independent human research projects which employ systematic data collection with the intent to contribute to generalizable knowledge.

13. Access/review of protected health information for research purposes. Protected health information belonging to Main Line Health, Main Line Hospitals, or other MLH Affiliate may not be used internally or disclosed to any persons or organizations outside MLH for research purposes without prior approval. Refer to the MLH IRB Policy on HIPAA-Use of Protected Health Information (PHI) for Research (XXIII).

14. Collaborative Research. Collaborative research requires IRB review by each site unless an IRB Authorization or Independent Investigator Agreement is in place.

15. Decedent Research. Access to protected health information of decedents requires IRB review and approval up to a period of 50 years following the death of the individual. Refer to the MLH IRB Policy on HIPAA: Use of Protected Health Information for Research (XXII).

B. Activities Not Subject to IRB Review include, but are not limited to:

1. Proposals that do not meet the definition of human subjects' research will not require IRB review.

2. Quality Assurance/Quality Improvement (QA/QI). Systematic, data-guided activities designed to implement promising ways to improve clinical care, patient safety and health care operations do not require IRB review. The activity is designed to bring about immediate positive changes in the delivery of health care, programs or business practices in the local setting and is not designed to develop or contribute to generalizable knowledge. QA/QI activities with research intent require IRB review.

3. Activities such as program and fiscal audits and certain disease monitoring as prescribed by the Public Health Department generally do not qualify as research.

4. Case Reports. A retrospective review of medical records for publication of a case report is not considered human research and does not require IRB review and approval. Generally, this involves three or less clinical cases and all data must be de-identified. Prospective intent to use data that would not ordinarily be collected in the course of treatment requires IRB review.

5. Innovative therapies/practice to provide diagnosis, preventative treatment or therapy to particular patients that does not involve research as previously defined. Care of a patient is considered research if there is clear intent before treating a patient to use systematically collected data which would not ordinarily be collected in the course of clinical practice in reporting and publishing a case study.

6. Coded private information or biological specimens that were not collected for the currently proposed projects do not need IRB review as long as the information cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. The investigators and the holder of the key enter into an agreement, generally referred to as a "honest broker" or data use agreement, prohibiting the

release of the key to the investigators under any circumstances. The agreement should be kept by the investigator and available for review when requested.

7. Public Health Activities where the purpose of the activity is to identify and control a health problem or improve a public health program or service; intended benefits of the project are primarily or exclusively for the participants, or clients, or the participants' community; data collected are needed to assess or improve the program or service, the health of the participants or the participants' community; knowledge that is generated does not extend beyond the scope of the activity; and project activities are not experimental.
8. Scholarly and journalistic activities, e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship, including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
9. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made disasters.
10. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
11. Authorized operational activities, as determined by each agency, in support of intelligence, homeland security, defense, or other national security missions.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. VI

Subject: CONVENED IRB REVIEW PROCESS

PURPOSE
This policy describes the convened IRB review process followed by the Main Line Hospitals (MLH) IRB for all studies which require review by the full Board.

A. Overview.
A majority of IRB members must be present at a convened IRB meeting that may only take place with a properly convened quorum of members, refer to the MLH IRB Policy on Overview of the Institutional Review Board (II). Items for review at a convened IRB meeting are assigned to two members of the committee, primary reviewers, by the Office of Research Protections (ORP) in cooperation with the Chair of the MLH IRB. At least one of the primary reviewers will be a physician or other experienced member with appropriate scientific or scholarly expertise. For protocols subject to FDA regulations, review by a licensed physician is required. Both primary reviewers are expected to perform an in-depth review of the research. The IRB will only review research when there is sufficient expertise to determine whether the applicable criteria for IRB approval are met.

B. Reviewer Expertise
ORP pre-reviews the protocol submission to determine the expertise required to provide scientific or scholarly review of the research. Primary reviewers are selected using the IRB roster and/or IRB members' CVs, see below. ORP staff consults with the IRB Chair when making reviewer assignments. The IRB Chair may reassign the review of research as appropriate. When making reviewer assignments, ORP staff and the IRB Chair consider the following:

- Reviewer's scientific and/or scholarly expertise
- Reviewer experience
- Reviewer's status as scientist or nonscientist
- Reviewer workload
- Potential conflicts of interest
- the need for special representation, e.g., vulnerable populations when regularly reviewed by the IRB and/or consultant when expertise is required beyond or in addition to that available on the IRB.

If ORP Staff, in consultation with the ORP Director and/or IRB Chair, believes that the IRB membership lacks sufficient expertise or experience to provide adequate review of the research or if the IRB member with the appropriate expertise/experience has a conflict of interest, the ORP Director and the IRB Chair will be responsible for obtaining a consultant.

Consultants may be scientists or non-scientists, internal or external to the organization and may be identified through communication with the relevant MLH Departments or by knowledge

of relevant local expertise. If necessary, consultants external to the organization may be sought. Consultants to the IRB may not have a conflict of interest in the research to be reviewed. Information provided by a consultant is documented in the IRB minutes. Any written reports provided by the consultant will be maintained in the ORP files in the relevant research files and information provided to the IRB at the meeting will be documented in the minutes. Consultants are given access to all documents relevant to the research and may participate in the discussion but may not vote.

C. Agenda

Research items for review at an upcoming meeting are placed on the agenda based on available expertise, members and consultants, order of submission, complexity, submission date, IRB workload and likelihood of a quorum if multiple IRB members are known to have similar conflicts of interest. The agenda lists other items to be reviewed at the meeting including any minutes from a prior meeting, educational article and expedited review/approval list. The agenda also serves as a guideline for the conduct of the meeting. The agenda for the meeting may include additional discussion items at the discretion of the IRB Chair or ORP Director.

D. Materials provided to IRB Members

IRB members are provided sufficient information so that each member can provide an opinion on whether the regulatory criteria for approval are met. Information is provided approximately one (1) week in advance of the meeting to IRB members and any alternate member scheduled to attend and at a minimum includes the items listed below. In addition, an agenda, the Expedited Approval list, to report those studies approved under expedited review, an educational article for IRB members and other topics, as required, are provided to each member or alternate member in attendance:

1. New Protocols:
    - ORP iMedRIS Application Forms, e.g., Protocol Submission Form, Initial Submission Form
    - Relevant IRB Reviewer Checklists for determinations specific to the study
    - Informed Consent/Assent/HIPAA Authorization Form(s)
    - Advertising/Recruiting Materials
    - Investigator Brochure, Package Inserts, Instruction for Use or other Device brochure, provided to IRB Chair and Primary Reviewers
    - IND, IDE, or Nonsignificant Risk/Significant Risk Determination Letters/Requests when applicable
    - Research Protocol
    - Relevant Grant Application(s), provided to the IRB Chair only
    - Conflict of Interest Management Plans
    - Additional information as provided by investigator or determined to be useful by ORP Staff and/or IRB Chair
    - Any previous IRB correspondence related to research
    - Any Information provided by consultant or primary reviewer in advance of meeting
    - For Department of Health and Human Services (DHHS) research, the DHHS sample consent document when one exists, provided to IRB Chair and Primary Reviewers

2. Requests for Continuing Review:
    - Requests for Continuing Review are submitted via iMedRIS and contain a status report on the progress of the research from the previous year
    - Relevant IRB Reviewer Checklists for determinations specific to the study
    - Approved Informed Consent/Assent Form(s) and any proposed changes to forms

- Research Protocol including any modifications previously approved, complete protocol provided to IRB Chair and Primary Reviewers; Synopsis provided to other IRB Members
- Relevant Grant Applications, when changes have been made to the grant application – provided to IRB Chair only
- Conflict of Interest Management Plan, when new or revised
- Additional information as provided by the investigator or determined to be useful by ORP Staff and/or IRB Chair
- IRB Correspondence during previous year, alternatively, summary may be submitted.
- Relevant post-approval reports including any unanticipated study-related events and any monitoring reports which have not been previously submitted to the IRB.
- Any Information provided by consultant or primary reviewer in advance of meeting
- Complete documentation is available to all members for review at their request.

3. Modifications:

- ORP iMedRIS Protocol Submission Form
- Relevant IRB Reviewer Checklists for determinations specific to the study
- Modified Informed Consent/Assent/HIPAA Authorization Form(s)
- Modified Research Protocol (complete revised protocol provided to IRB Chair and Primary Reviewers; Individual revised pages/summary of changes provided to other IRB Members)
- Modified Grant Applications, when changes have been made to the grant application provided to IRB Chair only
- Description of Modifications
- Additional information as provided by the investigator or determined to be useful by ORP Staff and/or IRB Chair
- Any Information provided by consultant or primary reviewer in advance of meeting
- Complete documentation is available to all members for review at their request.

4. Unanticipated Problems– refer to the MLH IRB Policy on Unanticipated Problems Involving Risks to Subjects or Others (XVIII)

iMedRIS “Adverse Event Reporting Form” for Unanticipated Problems and events which are Serious Adverse Events or Unanticipated Adverse Device Effects iMedRIS “General Reporting Form” form for all other events

- The form should contain:
  - A description of any changes made to the conduct of the study and any corrective actions to be taken by the investigator.
  - A clear explanation of why the event or series of events has been determined to meet the criteria for reporting.
- Approved Informed Consent/Assent Form(s)
- Current version of Research Protocol
- Additional information as provided by the investigator or determined to be useful by ORP Staff and/or IRB Chair

5. Serious or Continuing Noncompliance – refer to the MLH IRB Policy on Noncompliance (XX) for more information

6. Suspension of IRB approval determination made on an urgent basis by the Institutional Official (IO), IRB Chair/Vice-Chair or ORP Director – refer to the MLH IRB Policy on Suspensions or Terminations of IRB Approval of Research Policy (XXI) for more information

- Approved Informed Consent/Assent Form(s)

- Research Protocol
- Previous IRB Correspondence related to research when determined to be useful by ORP Staff and/or IRB Chair
- Any Information deemed relevant by ORP Staff and/or IRB Chair

E. Conditions for convened IRB meetings

A convened IRB meeting cannot occur unless the following conditions are met:

- A quorum consisting of the majority of the members is participating.
- At least one member is participating whose primary concerns are in nonscientific areas, i.e., a non-scientist.
- The appropriate expertise will be available at the meeting.
- All members are provided meeting materials and applicable IRB Reviewer Checklists in advance of the meeting.
- Any member may participate by teleconference or videoconference and can actively and equally participate in the discussion.
- A meeting may be convened by teleconference or videoconference, provided that a quorum of members participates. All members must be connected so they can actively and equally participate in the discussion.

F. Committee Actions During Meetings

When reviewing research, the convened IRB is responsible for determining the approval status and appropriate approval period, up to one year, of a study under review, and must notify the investigator of its decisions. The actions below are applicable when the convened IRBs conduct initial review, continuing review, or review of amendments to previously approved research. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting. If at any point during the meeting quorum is lost, no voting will take place until quorum is restored. The IRB has authority to approve, require modifications (to secure approval), or disapprove the research. The Committee's actions are communicated to the investigator and to ORP in writing and provided to the IO when required. ORP records IRB actions including the number of members voting for, against, abstaining, and those who have left the room because of a conflict of interest.

G. When reviewing research the convened IRB will take one of the following actions:

Approved: An IRB action taken when the required determinations are made that allow research involving human subjects to proceed consistent with federal regulations, state and local laws, and Main Line Health policy.

Require Modifications to Secure Approval: An IRB action that specifies conditions under which research can be approved, pending confirmation of specific understandings by the IRB about how the research will be conducted, submission of additional documentation, precise language changes to the protocol and/or informed consent document(s), and/or substantive changes to documents with specific parameters the changes must satisfy. Verification that the investigator's response(s) satisfies the conditions for approval set by the IRB may be performed by the IRB Chair, Vice-Chair, ORP Director, Designee(s), other member(s) empowered by the convened IRB or the convened IRB (when required). Items requiring substantive clarifications or modifications that are directly relevant to the determinations required by the IRB are tabled/deferred and must return to the Convened IRB for approval and may not be reviewed by outside a convened meeting.

Disapproved: An IRB action taken when the determinations required for approval of research cannot be made, even with substantive clarifications or modifications to the protocol and/or informed consent process/document. When research is disapproved, reasons for the decision

are provided to the investigator and a description of how investigators may respond, in person or in writing.

Tabled/Deferred: IRB action taken when the IRB cannot fully evaluate the research under review and make the determinations required for approval without modifications to the protocol and/or informed consent document, or submission of clarifications or additional materials. This term may also mean that the review was not initiated or was not completed, resulting in postponement of IRB review, usually due to loss of quorum or other administrative issue. Items requiring substantive clarifications or modifications that are directly relevant to the determinations required by the IRB are tabled/deferred. Any items which are tabled/deferred, along with the investigator's response(s) to any suggested changes must return to a convened IRB meeting for approval. The reason for this action is noted in the meeting minutes.

H. Approval Criteria (45 CFR 46.111, 116 and 117 and 21 CFR 50, 56.11)
In order for the IRB to approve a research protocol or plan at initial approval, at continuing review or review of modifications, the IRB must determine that all the criteria below are met. IRB members and staff are trained on the criteria.

1. risks to subjects are minimized by using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and whenever appropriate by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. risks to subjects are reasonable in relation to anticipated benefits, if any to subjects and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, defined by the Food and Drug Administration (FDA) and the Office of Human Research Protection (OHRP) as children, prisoners, pregnant women human fetuses and neonates. Additional protections may be considered for subjects who may be vulnerable to coercion or undue influence such as mentally disabled persons, economically or educationally disadvantaged persons, students and employees.
4. additional safeguards are in place when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women human fetuses and neonates, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. When applicable, the IRB must determine that additional protections of 45 CFR part 46 have been met:
    - 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)
    - Appropriate Additional Safeguards have been included in the protocol to protect the rights and welfare of other vulnerable subjects.

5. informed consent will be sought from each potential subject or the subject's legally authorized representative/surrogate in accordance with and to the extent required by 45 CFR 46.116 and 21 CFR 50.25.
6. informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117 and 21CFR 50.27.
7. when appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects Data and safety monitoring plans are generally not required for studies involving no more than minimal risk.
8. where appropriate, there are adequate provisions to protect the privacy of subjects. In making its determination, the IRB considered the reasonable expectations of privacy in relation to the research; the sensitivity and appropriateness of private information sought in relation to the research; potential for disclosure of private facts about subjects; and intrusive nature of the research procedures involved.
9. where appropriate, there are adequate provisions to maintain the confidentiality of data. In making its determination, the IRB considered the method(s) selected to maintain confidentiality of the data depending on the nature of the information collected and potential risk to subjects from a breach of confidentiality.
10. when some or all the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, human fetuses and neonates, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the protocol to protect the rights and welfare of these subjects. When applicable, the IRB must determine that the additional protections of 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), or subpart D (Additional Protections for Children Involved as Subjects in Research) of 45 CFR part 46 have been met.
11. use of Protected Health Information (PHI) will be obtained using a valid HIPAA Authorization form in accordance with 45 CFR 164.508 or waived in accordance with 45 CFR 164.512(i)(2)(ii).
12. when research involves adults unable to consent, the IRB determines that:
    - risks to the subjects (recognizing that some physical and social risks may be heightened in individuals with conditions that may cause diminished functional abilities) are reasonable in relationship to any anticipated benefits to subjects and to the importance of the knowledge that may reasonably be expected to result.
    - the population targeted for recruitment represents the population with the least degree of impairment to functional abilities compatible with the aims of the study.
    - appropriate procedures for assessing potential subjects' capacity to consent are described in the protocol.
    - the description of the informed consent process to be used is appropriate to the risk of the protocol as assigned by the IRB.
    - the appropriateness of the assent/surrogate consent and consent process described in the protocol for obtaining informed consent; and
    - all other aspects of the proposed research comply with the IRB Policy and Procedure Manual as appropriate.
13. for Continuing reviews, determines: the consent document is still accurate and complete; any new findings that arise from the review process and might relate to subject's willingness to continue participation will be provided to the subject and verification from sources other than the investigators that no material changes have occurred since previous IRB review. The IRB may determine it needs

verification when research involves unusual levels or types of risk to subjects, when concerns have been raised, through IRB review or from other sources, about possible material changes occurring without IRB approval or other circumstances for which the IRB deems independent verification is needed.

14. for modifications to previously approved research: determine if any new findings that arise from the review process and might relate to subject's willingness to continue participation will be provided to the subject.

I. Frequency of IRB Review

The IRB conducts continuing review for greater than minimal risk research at intervals appropriate to the degree of risk, but not less than once per year. The criteria used to consider whether more frequent review is required include, but are not limited to, the following:

- High-risk research there is concern about serious adverse events or research where the potential risks in humans are unknown and may have the potential to be serious (e.g., phase I drug study).
- Protocols with complex regulatory compliance requirements, such as emergency research.
- studies in which individuals with impaired decision-making capacity will be enrolled.
- studies for which there is little external oversight or data safety monitoring.

The period of IRB approval, whether annually or more frequently than annually, will be documented in the written minutes of the convened meeting. The approval notification sent to the investigator will specify the date IRB approval will expire.

J. Approval Dates

For new studies and continuing reviews, when no conditions/modifications are required to secure approval, the approval date is the date the research is approved at the convened IRB. Note: Approval dates assigned to continuing review will remain in line with current approval date time frame when protocol approval for renewal is within 30 days of expiration. When conditions/modifications are required to secure approval of a new study or a continuing review, the date the modifications/conditions are met by the investigator becomes the effective date of the IRB approval except for continuing review as above within 30 days of expiration

For modifications and amendments to approved research, when no modifications are required to secure approval, the approval date is the date the research is approved at the convened IRB. When conditions/modifications are required to secure approval, the date the modifications/conditions are met by the investigator becomes the effective date of the IRB approval.

K. Approval Period

The approval period for new studies and continuing reviews is the interval that begins on the day research is approved by the convened IRB when no changes are required. When conditions/modifications are required, to secure approval, the date that the modifications/conditions are met by the investigator becomes the effective date of IRB approval. The approval period is determined by the IRB and will not exceed one year from the date the research was reviewed by the convened IRB, i.e., this will result in an approval period of less than 1 year when modifications are required.

L. Expiration Date

The expiration date is the last date a protocol is approved. An expiration date may not be longer than one year from the date the approval period begins.

If research expires before all the conditions are reviewed and approved, all research activities must stop until approval is obtained.

M. Reporting of IRB Actions and Findings to the Investigator
The following information is reported in writing to the investigator after IRB review:

- The date of review
- What was reviewed
- The process of review by the convened IRB
- The decisions of the IRB
- If the IRB requires modification to the research protocol or plan to secure approval:
    - A description of the required modifications
    - The basis for requiring modification
    - How the IRB will review the modifications, by the IRB Chair or designee or by convened IRB
- If the IRB disapproves research:
    - A statement of the reasons for disapproval
    - A description of how investigators may respond in person or in writing

N. Investigator Response to IRB Findings
The investigator must address all IRB required revisions and requests. The investigator may appeal IRB required revisions to the protocol and/or consent form. All such appeals must be in writing and submitted to ORP for review by the Chair or the convened IRB when applicable. Any statement of disagreement should be accompanied by a written justification for the disagreement. If resolution is not possible between the Chair and the investigator the controverted issues would be returned to the convened IRB.

The investigator must include a copy of any revised documents including protocol and consent form with their responses with all changes highlighted using track changes.

An investigator may also appeal the IRB's decision to disapprove a study. Any statement of disagreement should be accompanied by a written justification for the disagreement. An appeal to have the IRB review a disapproved study must be made in writing and reviewed by the convened IRB. If the appeal is denied by the IRB, the IO or other official or committee may not override the IRB's decision.

O. Reporting of IRB Actions and Findings to the Institutional Official and Further Institutional Approval

The IO is notified of all findings of the IRB via the IRB minutes.

The Quality and Safety Committee (QSC) or other officials or committees may disapprove protocols approved by the IRB but may not approve protocols disapproved by the IRB.

Origination Date: 08/13/01
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. VII

Subject: EXPEDITED REVIEW PROCESS

This is a procedure through which the IRB Chair, Office of Research Protections (ORP) Director or their designees may exercise all of the authorities of the IRB to review certain research without convening the full IRB. Expedited review allows approval of a protocol by less than the convened IRB and may only be conducted by experienced IRB members with at least one (1) year experience on an IRB. Use of this procedure does not allow disapproval of the research by the reviewer.

Definition

Minimal risk - means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Applicability of Expedited Review

A. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the appropriate categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on the list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.
B. Categories apply regardless of the age of subjects, except as noted.
C. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.
D. The expedited review procedure may not be used for classified research involving human subjects.
E. The standard requirements for informed consent or its waiver, alteration, or exception, apply regardless of the type of review utilized by the IRB, i.e., expedited or convened IRB review process.
F. Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

Expedited Research Categories 1 through 9:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

Expedited Research Categories 1 through 9:

a. Research on drugs for which an investigational new drug application, 21 CFR Part 312, is not required. Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.
b. Research on medical devices for which (i) an investigational device exemption application, 21 CFR Part 812, is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling. *Note This category includes in vitro diagnostic devices.*

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   a. from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an eight (8) week period and collection may not occur more frequently than two (2) times per week; or
   b. from other adults and children[2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an eight (8) week period and collection may not occur more frequently than two (2) times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions, including sweat; (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization. Note: On October 4, 2010, the Office of Human Research Protection (OHRP) clarified that it agrees with the Food and Drug Administration's (FDA) position that the following procedures are considered noninvasive: Vaginal swabs that do not go beyond the cervical os; Rectal swabs that do not go beyond the rectum; and Nasal swabs that do not go beyond the nares.

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. Where medical devices are employed, they must be cleared/approved for marketing. Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications. Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical

Expedited Research Categories 1 through 9:

treatment or diagnosis). NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.

6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior, including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 4b. This listing refers only to research that is not exempt.
8. Continuing review of research previously approved by the convened IRB as follows:
   a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
   b. where no subjects have been enrolled and no additional risks have been identified; or
   c. where the remaining research activities are limited to data analysis.
9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Minor Changes in Approved Research: Minor Changes in Previously Approved Research During the Period, of one year or less for which Approval is Authorized

Examples of minor changes include editorial, study title, pagination, administrative, change of telephone number of contact person, or other minor changes in risk descriptions or protocol design that do not change overall risk/benefit ratio. Refer to the MLH IRB Policy on Modifications and Amendment Process (XVII) for a complete description of minor changes in previously approved research.

Materials for Review

Investigators are to submit the required materials, including all required supporting documentation as outlined on the IRB Policy and Procedures page, referencing section “IRB Submission Types”.

All documents outlined in the “Submission Types” section are provided to designated expedited reviewers.

Expedited Review Process

The IRB Chair and ORP Director or their designee(s) review the materials included with each submission. When reviewing requests for Continuing Reviews, a complete copy of the research protocol including any modifications previously approved is reviewed along with a status report on the progress of the research provided within the iMedRIS submission.

The IRB Chair and ORP Director or their designee(s) make the final determination of whether new protocol, requests for continuing review, amendment/modification or other items meet the eligibility criteria and falls into one or more of the expedited categories listed above. Eligibility of expedited review will be documented *within iMedRIS*. When the IRB Chair and ORP

Director have comments, they are provided in electronic form by ORP staff to investigators and/or study coordinator for a response.

The IRB Chair/designee may request additional review by other member(s) of the IRB with applicable expertise. The additional assigned reviewer provides comments in electronic form.

IRB Actions

The criteria used to approve a research protocol or plan at initial approval, at continuing review and review of modifications to research will comply with *Approval Criteria* in the MLH IRB Policy on Convened IRB Review Process (VI).

The IRB Chair and ORP Director or their designee(s) may exercise all of the authorities of the IRB including approval and requiring modifications to secure approval except that the reviewer(s) may not disapprove the research. If the reviewer finds that the research should not be approved it must be referred to the convened IRB for final determinations. The reviewer may determine that the submission may not be expedited. The reviewer may also decide that additional information must be provided by the investigator prior to review by the convened Board. The IRB Chair and ORP Director or their designee(s) may choose to consult with another member prior to making any determinations.

When modifications are required, verification that the investigator's response(s) satisfies the conditions for approval set by the IRB may be performed by the IRB Chair, Vice Chair, ORP Director, their designee(s) or the convened IRB, when required.

All items approved by Expedited Review are reported to the convened IRB meeting on the *Items Approved by Expedited Review* summary which is provided to each member.

Designation of Reviewers Other Than an IRB Chair

By virtue of the qualifications and experience necessary for the position, the IRB Chair, Vice Chair(s) and ORP Director are eligible to review on an Expedited basis. If needed to address considerations such as expertise, scheduling or submission volume, an IRB Chair or Vice Chair may identify other experienced members with at least one year of service.

Investigator Response to IRB Findings

The investigator must address all IRB-required revisions and requests. The investigator may appeal IRB-required revisions to the protocol and/or consent form. All such appeals must be in writing and submitted to ORP for review by the Chair or the convened IRB when applicable. Any statement of disagreement should be accompanied by a written justification for the disagreement. If resolution is not possible between the Chair and the investigator, the controverted issues would be returned to the convened IRB.

The investigator must include a copy of any revised documents including protocol and consent form with their responses with all changes highlighted (using track-changes).

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. VIII

Subject: EMERGENCY/EXPANDED ACCESS USE OF AN INVESTIGATIONAL TEST ARTICLE

POLICY

The emergency use provision in Food and Drug Administration (FDA) regulations is an exemption from the requirements for prior review and approval of research by the IRB. The exemption, which must meet the specific conditions described in the regulations, allows for one (1) emergency use of an investigational drug or biologic or unapproved medical device in a life-threatening situation for which no standard acceptable treatment is available and when there is not sufficient time to obtain IRB approval.

This policy outlines the requirements for emergency uses of investigational drugs or biologics, emergency uses of unapproved medical devices, and exceptions to the requirements for informed consent in emergency situations.

DEFINITIONS

1. Emergency Use: Use of an investigational drug or biologic or unapproved medical device for a human subject in a life-threatening situation for which no standard acceptable treatment is available when there is not sufficient time to obtain IRB approval.
2. Unapproved Medical Device: A device used for a purpose or condition for which the device would require but does not have premarket approval or an approved investigational device exemption (IDE) from FDA.
3. Investigational Device Exemption (IDE): An application that permits a medical device that would otherwise be required to comply with an existing performance standard or to have premarket approval by FDA to be legally shipped for a clinical investigation.
4. Investigational New Drug (IND) Application: An application that permits an investigational drug that would otherwise be required to have premarket approval by FDA to be legally shipped for a clinical investigation.
5. Compassionate Use (Expanded Access): Use of an investigational drug or biologic or unapproved medical device for a single subject, or small group of subjects, with a serious disease or condition, who does not meet the requirements for inclusion in a clinical investigation, and for whom no standard acceptable treatment is available. Prior FDA and IRB approval are required for compassionate use. Note: The terms compassionate use and emergency use are not synonymous.
6. Life-threatening: Refers to diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; also diseases or conditions with potentially fatal outcomes.

7. Severely Debilitating: Refers to diseases or conditions that cause major irreversible morbidity, e.g., blindness, loss of limb, loss of hearing, paralysis, or stroke.

GENERAL INFORMATION

a. Only one emergency use of the test article is permitted and any subsequent use needs to be done under an IRB approved protocol. Any subsequent use[6] of the test article at MLH is subject to IRB review and approval.
b. Patients receiving the emergency use of an investigational drug, biologic or unapproved medical device are generally not considered research subjects and data obtained from patients may not be classified as human research and may not be included in any report of research activities subject to the Department of Health and Human Services (DHHS) regulations.
c. IRB approval is required prior to conducting human subject research. However, an exception to this is the one-time use of an investigational drug or device, test article, for a single subject in a life-threatening, emergency use, situation.
d. The use of a marketed drug, biologic, or medical device for an indication that is not listed in the FDA-approved product labeling, i.e., "off label" use, for an individual in a life threatening situation does not constitute an emergency use as defined by FDA regulations.
e. FDA requirements for emergency uses of investigational drugs and biologics differ slightly from the requirements for emergency uses of unapproved medical devices, as described below.

CRITERIA FOR EMERGENCY USE

According to FDA regulations, the emergency use exemption may be used if all the following conditions are met:

- The use involves an investigational drug or biologic, unapproved medical device, or other "test article" as defined by FDA
  - A test article is any drug, biologic, or medical device for human use or any other article subject to FDA regulations
- The individual for whom the test article is intended is in a life-threatening situation
  - To meet the criteria for life threatening a condition does not have to be immediately life-threatening or immediately resulting in death
  - Life-threatening also includes "severely debilitating"
  - Severely debilitating does not include "pre-existing", e.g., chronic, diseases or conditions with major morbidity
- No standard acceptable treatment is available
  - Also, the individual for whom the test article is intended does not meet the enrollment criteria for an existing IRB-approved study or an approved study does not exist
- There is not sufficient time to obtain IRB approval
  - An intervention is needed before review at a convened meeting of the IRB is feasible

[6] FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. (FDA Information Sheet, 2003 Update). Investigators are encouraged to evaluate the likelihood of a similar need occurring again, and if future use is likely, immediately initiate efforts to obtain IRB review and approval of a protocol to permit further use of the investigational drug, biologic, or device.

INVESTIGATOR'S RESPONSIBILITIES

If time permits, notify the IRB Office of the intended Emergency Use.

A. Investigators/treating physician may contact the IRB Chair, or physician designee, or the Office of Research Protections (ORP) via phone or email. The following information should be provided:
    i. Explanation of the life-threatening situation necessitating the emergency use
    ii. Description of standard treatment(s) previously used and/or why available options are not acceptable
    iii. Investigational drug or biologic or unapproved medical device to be used
    iv. If available, IND or IDE number of the drug, biologic, or device.

Note: This notification should not be construed as an IRB approval. The investigator's notification is used to confirm that the proposed use meets FDA requirements and to assist the investigator with filing the required report within the five-day timeframe required by FDA regulations.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. The IRB can prepare a written statement that the IRB is aware of the proposed use and a preliminary determination has been made which considers the use to meet the requirements of 21 CFR 56.104(c). NOTE: The acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

Investigator responsibilities before the test article is used:

1. The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.
    - If a drug or biologic will be used, the investigator must obtain an emergency IND. The usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND. If there isn't time to apply for an IND, the FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means to the FDA.
2. FDA approval prior to emergency use or shipment of an unapproved medical device is not required. The emergency use may involve a device that does not have an existing IDE, a device used in a way that is not approved under an existing IDE, or a physician who is not named as an investigator on the IDE. Whenever possible, authorization should be obtained from the sponsor (if an IDE exists for the device) before the emergency use.
    - In addition to determining that the criteria for emergency use are met, investigators are required by FDA to assess the potential for benefit from the use of an unapproved device and to have "substantial reason" to believe that benefits will occur. Whenever possible, an independent assessment of the circumstances prior to the emergency use should also be obtained from a physician who is not otherwise involved in the emergency use.
    - If the device has an existing IDE and the investigator could not obtain authorization from the sponsor prior to the emergency use, the investigator is responsible for reporting to the sponsor within five working days.

- If no IDE exists, the investigator is responsible for reporting the emergency use directly to FDA. The investigator's responsibilities to submit the follow-up report should contain the information described further below.

For the use of an investigational Device, the physician should follow as many patient protection measures as possible. This includes obtaining:

- Informed consent from the subject or the subject's legally authorized representative in an emergency use situation. All of the basic elements of informed consent and any applicable additional elements are to be provided, unless the situation meets the conditions for exception described under Informed Consent Requirements
- Clearance from the institution as specified by applicable MLH policies
- Concurrence of the IRB Chair.
- An independent assessment from an uninvolved physician; and
- Authorization from the IDE sponsor, if an approved IDE exists for the device.

Informed consent requirements

For emergency use of a drug, biologic or device, the investigator is required to obtain written informed consent of the subject or the subject's legally authorized representative.

Written informed consent does not have to be obtained if both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

- The subject is confronted by a life-threatening situation necessitating the use of the test article
- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject
- Time is not sufficient to obtain consent from the subject's legal representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

NOTE: If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within five (5) working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is NOT participating in the clinical investigation.

Investigator Responsibilities after the test article is used:

The investigator must notify the IRB within five (5) working days after the use of the test article [21 CFR 50.23(c)] and documentation should contain:

- Description of the test article that was used, including any IND or IDE numbers
- Description of conditions necessitating the emergency use
- The date of administration of the investigational product
- Patient initials and demographics
- The status of the patient
- An unsigned copy of the consent form when one was used
- Confirmation that written consent (when applicable) or when written consent was not obtained, provide written certification from the investigator and a physician who was not otherwise participating in the clinical investigation that:

- The subject is/was confronted by a life-threatening situation necessitating the use of the test article
- Informed consent was not/cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject
- Time is/was not sufficient to obtain consent from the subject's legal representative
- No alternative method of approved or generally recognized therapy is/was available that provides an equal or greater likelihood of saving the subject's life

- FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. If the investigator believes the investigational product may need to be used again a new protocol submission should be submitted to the IRB. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Investigators are also responsible for reporting the circumstances of the emergency use to the product manufacturer or sponsor of the investigational drug or biologic or unapproved medical device when the emergency use was performed under the manufacturer's/sponsor's IND or IDE. Otherwise, the emergency use is reported directly to FDA. The follow-up report should contain the following information:

- Summary of the conditions constituting the emergency
- Acknowledgment by the IRB Chair of prior notification of the emergency use
- Whether informed consent was obtained or the conditions were met for the exception to the requirements for informed consent
- Independent assessment by a physician not otherwise involved in the clinical investigation (when applicable)
- Outcome(s) of the emergency use
- Other information as required by the product manufacturer or sponsor.

Investigators who obtain an IND or IDE for the emergency use or subsequent use of the investigational drug or biologic or unapproved medical device are responsible for complying with FDA requirements for the use of investigational drugs and devices, including providing progress and/or final reports.

IRB REQUIREMENTS

The IRB Chair, or physician designee, will review emergency use reports within 14 days of receipt to determine that the circumstances met FDA requirements.

- If the emergency use meets the criteria allowing an exemption from prior IRB review and approval, a letter will be issued to document the findings.
- If the emergency use did not meet the criteria allowing an exemption from prior IRB review and approval the matter will be handled according to the MLH IRB Policy on Noncompliance (XX).

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **IX**

Subject: **EXPANDED ACCESS TO FDA-REGULATED INVESTIGATIONAL TEST ARTICLES**

NOTE: Expanded Access is an evolving regulatory landscape. Prior to making an expanded access request, please refer to the FDA Expanded Access website for the Agency's current thinking and requirements.
https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

POLICY

It is the policy of the Main Line Hospitals Institutional Review Board (MLH IRB) to review expanded access requests of Food and Drug Administration (FDA) regulated investigational agents, including drugs, devices, and biologics.

GENERAL INFORMATION

Expanded access, sometimes called "compassionate use," is the use outside of a clinical trial of an investigational medical product, i.e., one that has not been approved by FDA.
Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), a patient may seek individual patient expanded access to investigational products for the diagnosis, monitoring, or treatment of a serious disease or condition when the following conditions are met:

- The patient and a licensed physician are both willing to participate.
- The patient's physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient's disease or condition.
- That the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
- FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance.
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.
- The sponsor, generally the company developing the investigational product for commercial use, or the clinical investigator, or the patient's physician in the case of a single patient expanded access request, submits a clinical protocol, a document that describes the treatment plan for the patient, that is consistent with FDA's statute and applicable regulations for Investigational New Drugs (INDs) or investigational device exemption applications (IDEs), describing the use of the investigational product; and
- The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial.

DEFINITIONS

1. Expanded access: sometimes called "compassionate use," is the use outside of a clinical trial of an investigational medical product, i.e., one that has not been approved by FDA.

2. Immediately life-threatening disease or condition: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

3. Serious disease or condition: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Information below is excerpted from the FDA Expanded Access Website at: *https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm*

TYPES OF EXPANDED ACCESS

1. Expanded Access to Investigational Drugs[7] and Biologics
    a. 21 CFR part 312 subpart I provides general requirements, describes criteria that must be met to authorize expanded access, lists requirements for expanded access submissions, and describes safeguards that will protect patients and preserve the ability to develop meaningful data about the use of the investigational product.
    b. Under FDA's current regulations for investigational drugs and biologics, there are three categories of expanded access:
        i. Expanded access for individual patients, including for emergency use;
        ii. Expanded access for intermediate-size patient populations; and
        iii. Expanded access for widespread use.

2. Expanded Access for Medical Devices
    a. Emergency use is the use of an investigational device in an emergency situation. It is intended to provide patients and physicians with access to devices intended to treat life-threatening or serious diseases or conditions when there is no available alternative and no time to obtain FDA approval. Emergency use may apply even if the investigational device is being studied in a clinical trial under an IDE: if a physician needs to use the device in a manner inconsistent with the approved investigational plan; or a physician who is not part of the clinical study, wishes to use the device to treat a patient with a life-threatening or serious disease or condition. Emergency use of an investigational device may occur before an IDE is approved and when a device is not being studied under an IDE.
        i. Criteria:
            1. The patient has a life-threatening or serious disease or condition that needs immediate treatment,

[7]Pending implementation of the Right to Try Act of 2017 (S.204), signed into law of 05/30/18, which amends the Federal Food, Drug, and Cosmetic Act to exempt, from specified requirements and restrictions under that Act and other laws, the provision of certain unapproved, investigational drugs to a terminally ill patient.

2. No generally acceptable alternative treatment for the condition exists; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

b. Individual Patient/Small Group Access provision provides a path to accessing investigational devices that have not received FDA approval or clearance for patients for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. This may be used for devices that are being studied in a clinical trial under an IDE for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation, i.e., an IDE for the device does not exist. This provision is typically approved for individual patients but may be approved to treat a small group.
    i. Criteria:
        1. The patient has a life-threatening or serious disease or condition, and
        2. No generally acceptable alternative treatment for the condition exists.

c. Treatment Use provision of the IDE facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. A device that is not approved for marketing may be under clinical investigation for a serious or immediately life threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the treatment IDE regulations. (21 CFR §812.36)
    i. Criteria:
        1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition.
        2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population.
        3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed, and
        4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

REQUIREMENTS

A. Drug or Biologics

Expanded Access to an Investigational Drug/Biologic Under a Single Patient IND

Individual patient expanded access submissions made by individual physicians are submitted as new INDs. If a licensed physician is making the individual patient expanded access submission, he or she also must be willing to manage the use of the investigational drug and the patient's medical care.

Physicians should:

1. Apply for expanded access to an investigational drug under a single patient IND. Form FDA 3926 can be used by physicians when submitting requests for individual patient expanded access to investigational drugs, including in emergencies. This form is designed specifically for single patient IND requests.
2. Ask the medical product company for a Letter of Authorization (LOA), if applicable. An LOA from a company allows the physician submitting the single patient IND to satisfy some of the submission requirements by relying on information in the company's existing IND. It also authorizes FDA to refer to the company's IND when reviewing the single patient IND.
3. Complete the necessary paperwork and submit the request to FDA.
4. Obtain Institutional Review Board (IRB) review and approval, consistent with 21 CFR part 56. A physician submitting an individual patient expanded access IND using Form FDA 3926 may select the appropriate box on that form to request authorization to obtain concurrence by the IRB Chair or by a designated IRB member before the treatment use begins, in lieu of obtaining IRB review and approval at a convened IRB meeting at which a majority of the members are present. Although Form FDA 1571 does not include a specific field for making such a request, a physician submitting an individual patient expanded access IND using Form FDA 1571 may include a separate request with the application.
5. Review the requirements for expanded access with the patient and obtain informed consent.
6. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment may begin.

Individual Patient Expanded Access Protocol (also referred to as a Single Patient Protocol):

Access to an investigational drug, including a biologic, for use by a single patient submitted as a new protocol *to an existing IND by the sponsor of the existing IND*. Typically, several patients may follow the same protocol. The investigational product may or may not be under development. There is no 30 day waiting period before treatment with the investigational product may begin, but the protocol must be received by FDA and have approval by an IRB before treatment may begin.

Intermediate-size Patient Population Expanded Access IND:

Access to an investigational drug, including a biologic, for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol *under a new IND*. The investigational product may or may not be under development for marketing. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30-day waiting period before treatment may begin.

Intermediate-size Patient Population Expanded Access Protocol:

Access to an investigational drug, including a biologic, for use by more than one patient, but generally fewer patients than are treated under a typical treatment IND or protocol, submitted as a protocol *to an existing IND by the sponsor of the existing IND*. The investigational product may or may not be under development for marketing. There is no 30-day waiting period before

treatment with the investigational product may begin, but the protocol must be received by FDA and have IRB approval before treatment may begin.

An intermediate size patient population protocol may also be requested to allow access to treatment with an approved drug, including a biologic, or a related product that is not available through marketing channels because of failure to meet the conditions of approval or a drug shortage, provided the drug and the patient meet the general criteria for expanded access as well as the criteria specific to use in an intermediate size patient population.

Expanded Access for Widespread Use

Treatment IND:

Access to an investigational drug, including a biologic, for treatment use by a large, widespread, population, submitted as a protocol *under a new IND*. The investigational product must be under active development for marketing. Unless FDA notifies the sponsor that treatment may begin earlier, there is a 30 day waiting period before treatment may begin.

Treatment Protocol:

Access to an investigational drug, including a biologic, for treatment use by a large, widespread, population, submitted as a protocol *to an existing IND by the sponsor of the existing IND*. The investigational product must be under development for marketing. Unlike other access protocols submitted to existing INDs, there is a 30-day waiting period before treatment may begin, unless FDA notifies the sponsor that treatment may begin earlier.

B. Devices

Expanded Access to Investigational Medical Devices

There may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient or to help a patient suffering from a serious disease or condition for which no other alternative therapy exists. If a licensed physician would like to obtain an investigational device for an individual patient, the medical device company must first agree to provide the investigational device. FDA cannot require a company to provide an investigational device for compassionate use to proceed. If the device manufacturer agrees to provide the device, there are two different processes to follow to obtain FDA approval, depending on whether or not there is an IDE for a clinical trial for that device.

1. If there is an IDE for the device, the IDE sponsor, who may be the device manufacturer or a physician who has submitted the IDE to conduct the clinical study for the device, should submit an IDE supplement requesting approval for the use under section 21 CFR §812.35(a) in order to treat the patient. The IDE supplement should include:

- A description of the patient's condition and the circumstances necessitating treatment,
- A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition,
- An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient,
- The patient protection measures that will be followed:
    - A draft of the informed consent document that will be used,
    - Clearance from the institution as specified by their policies,
    - Concurrence of the IRB Chair,

- An independent assessment from an uninvolved physician, and
- Authorization from the device manufacturer on the use of the device.

In some cases, the IRB will not approve the request until they have approval from FDA. In such cases, the original request should indicate that IRB approval will be obtained prior to use of the device. Proof of the approval by the IRB Chairperson will need to be submitted with the follow-up report after the patient is treated. The physician should ask the IRB or risk management staff if institutional clearance is needed in addition to the IRB Chair concurrence.

2. If there is no IDE for the device, the physician or manufacturer submits the above information to FDA, along with a description of the device provided by the manufacturer.

The physician should not treat the patient identified in the request until FDA approves use of the device under the proposed circumstances. In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device.

The above criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from a serious disease or condition for which no alternative therapy adequately meets their medical need. In this case, the request should include the information identified above and indicate the number of patients to be treated. If there is an IDE for the device, the supplement should include the protocol to be followed or should identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in a report after all compassionate use patients have been treated.

FDA Actions

After a compassionate use request is received, FDA will approve, approve with conditions, or disapprove the request. When there is an IDE for the device, compassionate use request IDE supplements have the same statutory 30 day review cycle as other IDE submissions. However, the patient need is considered when reviewing these requests and they are often expedited if necessary.

Reporting Requirements

Following the compassionate use of the device, a follow-up report should be submitted by whoever submitted the original compassionate use request to FDA. This report should present summary information regarding patient outcome. If any problems occurred as a result of device use, these should be discussed in the follow-up report and reported to the reviewing IRB as soon as possible.

Treatment Use of a Device

An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the

data suggest that the device is effective, then the trial may be expanded to include additional patients with life threatening or serious diseases.

A device that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of the treatment IDE regulations.

The treatment use provision of the IDE facilitates the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device's safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under this section after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under this section prior to the completion of all clinical trials.

How does a sponsor apply for a Treatment Use IDE?

A treatment IDE application must include items noted below, in the following order:

1. The name, address, and telephone number of the sponsor of the treatment IDE,
2. The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use,
3. An explanation of the rationale for use of the device, including, as appropriate, either a list of the available regimens that ordinarily should be tried before using the investigational device or an explanation of why the use of the investigational device is preferable to the use of available marketed treatments,
4. A description of clinical procedures, laboratory tests, or other measures that will be used to evaluate the effects of the device and to minimize risk,
5. Written procedures for monitoring the treatment use and the name and address of the monitor,
6. Instructions for use for the device and all other labeling as required under section 21 CFR §812.5(a) and (b),
7. Information that is relevant to the safety and effectiveness of the device for the intended treatment use. Information from other IDEs may be incorporated by reference to support the treatment use,
8. A statement of the sponsor's commitment to meet all applicable responsibilities under the IDE regulations (21 CFR 812) and Institutional Review Boards regulations (21 CFR 56) and to ensure compliance of all participating investigators with the informed consent requirements of 21 CFR 50,
9. An example of the agreement to be signed by all investigators participating in the treatment IDE and certification that no investigator will be added to the treatment IDE before the agreement is signed, and
10. If the device is to be sold, the price to be charged and a statement indicating that the price is based on manufacturing and handling costs only.

A licensed practitioner who receives an investigational device for treatment use under a treatment IDE is an "investigator" under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56.

FDA actions on Treatment IDE applications

Treatment use may begin 30 days after FDA receives the treatment IDE submission. FDA may notify the sponsor in writing earlier than the 30 days that the treatment use may or may not begin. FDA may approve the treatment use as proposed or approve it with modifications.

IRB RESPONSIBILITES

For all expanded access use prior IRB review and approval, or concurrence by the IRB Chair, is needed as well as prior approval from the FDA, when applicable and a letter of authorization from the company. Emergency use does not require prospective IRB approval but there are specific criteria that must be met. Refer to MLH IRB Policy on Emergency Use of an Investigational Test Article (VIII).

NOTE: Expanded Access is an evolving regulatory landscape. Prior to making an expanded access request, please refer to the FDA Expanded Access website for the Agency's current thinking and requirements.
https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. X

Subject: HUMANITARIAN USE DEVICE/HUMANITARIAN DEVICE EXEMPTION

POLICY

It is the policy of the Main Line Hospitals Institutional Review Board (MLH IRB) to review and approve the use of Humanitarian Use Devices (HUD) within their approved labeling.

DEFINITIONS

Humanitarian Use Device: A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects not more than 8,000 individuals[8] in the United States per year. The use of a HUD is not considered research and a research protocol is not required for use of a HUD.

Humanitarian Device Exemption (HDE): A Food & Drug Administration (FDA) approval of an HDE permits the marketing of a HUD. Approval of an HDE requires evidence of safety and probable benefit but does not require establishing effectiveness. Data can be collected in a clinical investigation for the HDE approved indications without an Investigation Device Exemption (IDE). Clinical investigations of a HUD for a different indication than the HDE approved indication must be conducted in compliance with the IDE regulations (21CFR 812) and are not subject to this policy.

IRB REVIEW OF HUD

In order for a HUD to be used at the institution within its approved indication(s), the HUD must have an approved HDE from the FDA and IRB approval.

1.) Initial IRB review and approval must be conducted at a convened meeting. The IRB may approve use of the HUD without any further restrictions, or under a protocol, or on a case by case basis. The convened IRB may make the determination at initial review or at a subsequent convened IRB meeting, that continuing review may occur using the expedited procedure. All IRB members are provided the following information at the time of initial review:

- Device description, including the HDE number
- Copy of the FDA Approval Letter
- Product labeling
- Consent form when applicable
- Patient information packet which may accompany the HUD

[8] On 12/13/16, Section 3052 of the 21st Century Cures Act (Pub. L. No. 114-255) changed the population estimate required to qualify for Humanitarian Use Device (HUD) designation from "fewer than 4,000" to "not more than 8,000."

- Additional information as provided by investigator or determined to be useful by ORP Staff and/or IRB Chair when necessary

The IRB may impose more stringent restrictions for use of the HUD as a means of ensuring additional protection as deemed necessary. For example, the IRB may require re-review at an interval of time more frequent than annually or may want to conduct re-review after a specified number of patients have been accrued.

2.) Use of a consent form is not required unless the use represents a clinical investigation, however the IRB may require that one is used in all cases, and requires that information on the use of the HUD be provided to patients, e.g., patient information packet or information. The IRB may determine what is required for the use of a specific HUD on a case by case basis.

    Note: Collection of safety and effectiveness data to support a premarket approval (PMA) application by the HDE holder for the HDE approved indication may occur under the HDE without the need to obtain an IDE. However, the activity is considered a clinical investigation rather than clinical practice and, as with other FDA regulated clinical investigations, IRB approval and informed consent are required.

3.) Use of the HUD must undergo continuing review at least annually by the IRB and may perform this review by expedited review. Criteria for subsequent continuing review using the expedited procedure may include: unanticipated problems, complaints, medical device reports and any additional risks which may have been identified.

4.) Modifications to the HUD or proposed changes require IRB review and approval. All IRB members are provided the following information as applicable:
    - iMedRIS amendment to protocol submission form
    - Copy of FDA Approval Letter of the modification
    - the HDE holder's amendments to the HUD product labeling, clinical brochure, and/or other pertinent materials corresponding to the requested modification(s)
    - Revised consent form or equivalent, when applicable
    - Revised protocol, when available
    - Additional information as provided by the physician

PHYSICIAN RESPONSIBILITIES

The Physician is responsible to provide all necessary materials for IRB review and to obtain IRB approval prior to the first use of the HUD. The Physician is responsible for ensuring the HUD is used within the scope of its approved labeling and only by appropriately trained individuals. The Physician must provide all applicable information regarding the use of the HUD in his/her application materials submitted to the IRB which includes:

- ORP Forms, e.g., iMedRIS Protocol Submission Form, a list of those individual who will use the HUD
- Device description, including the HDE number
- Copy of FDA Approval Letter
- Product labeling
- Sample Consent form, when applicable
- Protocol, when applicable
- Patient information packet that may accompany the HUD
- Additional information determined to be useful by the Physician

After obtaining IRB approval, the Physician utilizing the HUD for treatment and/or diagnosis must use the HUD only in accordance with the labeling of the device.

The Physician will fulfill continuing review requirements at the designated IRB intervals. At each continuing review the Physician/investigator will provide the following information to the IRB:

- ORP iMedRIS Continuing Review Submission Form that contains a status report of the previous year including:
  - unanticipated problems that are serious adverse events or unanticipated adverse device effects
  - any medical device reports (MDS) as required under 21 CFR 803
  - complaints
  - any additional risks which may have been identified

All modifications to the HUD or proposed changes to the clinical use of the device must be submitted for IRB review and approval. The amendment application should include as applicable:

- ORP iMedRIS Protocol Submission Form
- Copy of FDA Approval Letter of the modification
- the HDE holder's amendments to the HUD product labeling, clinical brochure, and/or other pertinent materials corresponding to the requested modification(s)
- Revised consent form or equivalent, when available
- Revised protocol, when available

OFF-LABEL AND EMERGENCY USE OF A HUD

1.) Off-label, i.e., use for a non-HDE approved indication, use of the HUD requires review and approval by the convened IRB on a case-by-case basis except for emergency use (see Item 2 below).

A HUD may be used "off-label" for clinical care with prior FDA approval and by complying with the FDA expanded access, compassionate use, for unapproved devices. Refer to the MLH IRB Policy on Expanded Access to FDA Regulated Investigational Test Articles (IX) for more information.

Research conducted on off-label uses of HUDs must follow all requirements in 21 CFR 812, 50 and 56 and requires prior submission to the FDA for an IDE and cannot be approved under this policy.

2.) For use of HUD in an off-label, life-threatening emergency, refer to the MLH IRB Policy on Emergency Use of an Investigational Test Article (VIII).

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XI

Subject: EXEMPT REVIEW PROCESS

POLICY
All research activities involving humans as research subjects must be reviewed and approved by the MLH Institutional Review Board (IRB) unless the IRB Chair, Office of Research Protections (ORP) Director or their designees determines that the research falls into one or more of the categories of exemption established by federal regulations.

At Main Line Health, only the MLH IRB and ORP may determine which activities qualify for exempt status. Investigators do not have the authority to make an independent determination that research involving human subjects is exempt and must contact the IRB or ORP.

Exempt Research Categories
Research that qualifies for exemption from the requirements of federal regulations 45 CFR 46.104 or 21 CFR 56.104, including continuing review by the IRB, is determined when the only involvement of human subjects will be in one or more of the following eight categories:

1. Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research that only includes interactions involving educational tests, cognitive, diagnostic, aptitude, achievement, survey procedures, interview procedures, or observation of public behavior, including visual or auditory recording, if at least one of the following criteria is met:
   (i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects,
   (ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   (iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 45 CFR 46.111(a)(7)*

Note: Exempt Categories 2(i) and (ii) only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (2(iii) may not be applied to research subject to subpart D.

*When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

3. Research involving benign behavioral interventions** in conjunction with the collection of information from an adult subject through verbal or written responses, including data entry, or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:
(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects,
(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation, or
(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §ll.111(a)(7)***. If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

**Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing.

***When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
(i) The identifiable private information or identifiable biospecimens are publicly available,
(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects,
(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of ''health care operations'' or ''research'' as those terms are defined at 45 CFR 164.501 or for ''public health activities and purposes'' as described under 45 CFR 164.512(b), or
(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with

section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

5. Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads, or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects, and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended. (i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies:
   (i) If wholesome foods without additives are consumed, or
   (ii) 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 (FDA) or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

7. Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §ll.111(a)(8). NOTE: Broad Consent has not been adopted at Main Line Health. [9]

8. Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:
   (i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §ll.116(a)(1) through (4), (a)(6), and (d),
   (ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §ll.117,
   (iii) An IRB conducts a limited IRB review and makes the determination required by §ll.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and
   (iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding

[9] Broad consent will be further evaluated when compliance with technical and regulatory requirements can be confirmed. Additional guidance will be developed at that time.

by any legal requirements to return individual research results. NOTE: Broad Consent has not been adopted at Main Line Health[9].

Research which is Not Exempt
Research that does not qualify for IRB exemption includes, but is not limited to the following types:

- Research involving prisoners.
- Research in Exempt Categories 2(i) and (ii) only may apply to research subject to subpart D involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Paragraph (2(iii) may not be applied to research subject to subpart D.
- Research which involves deception that is not disclosed prospectively.
- Research involving decisionally impaired individuals.
- Sensitive topics, such as illegal conduct, drug use, sexual behavior or use of alcohol
- Research which is subject to FDA regulations *except* as defined in Exempt Category 6.

Investigator Responsibilities
The investigator will make a preliminary assessment that a proposal is eligible for exemption based on the regulatory criteria and submit an application for IRB review. The investigator will not begin the project until the exempt status is confirmed in writing.

To ensure a complete review, a description of the planned research, i.e., a research protocol, or written description, must be submitted. The written study description should include study objectives, plan for conducting the research including a study recruitment plan, discussion of how the research findings will be analyzed, a description of the provisions to protect the privacy of subjects and to maintain the confidentiality of data. There is no required consent template for exempt research. However, specific elements of informed consent should be included in consent forms or scripts as applicable.

When an exemption determination is made it is effective for the life of the study unless modifications have been made. All modifications to a study that has been determined to be exempt must be submitted to the IRB/ORP for prospective review prior to implementation. In some circumstances, changes to the protocol may disqualify the project from exempt status. Note: Studies which receive an exempt determination after 01/21/19 require an annual check-in. Providing an annual study check-in is the responsibility of the principal investigator and will require an update on study status, participating personnel and CITI training status.

Ethical Standards of Exempt Research
Generally, the criteria used for a particular research protocol or plan will be a subset of the criteria used by the convened IRB and for example will generally include:

- The research involves no more than minimal risk to subjects.
- Selection is equitable.
- There are adequate provisions to maintain the privacy interests of subjects.
- If there are interactions with subjects, there will be a consent process that will disclose such information as:
    - That the activity involves research.
    - A description of the procedures.
    - That participation is voluntary.
    - Name and contact information for the investigator.

Review and Documentation
IRB Chair, ORP Director or their designee(s) will review requests of exemption submitted by investigators, generally within 1 week of submission. Determinations of eligibility for Exemptions and appropriate Ethical Standards are documented on the *Exempt Reviewer Checklist within iMedRIS.*

Determinations of exempt status are communicated to an investigator in writing via iMedRIS and will document the Exempt Category(s) determined to be applicable. When a research project has been determined to be exempt from IRB review, an annual study check-in is required.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XII

Subject: INFORMED CONSENT REQUIREMENTS AND DOCUMENTATION

POLICY

Unless waived by the IRB, legally effective informed consent must be obtained from a subject or the subject's legally authorized representative (LAR) prior to their participation in research. The investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR. The IRB requires documentation of informed consent by use of a written consent form approved by the IRB and signed, as well as dated, by the subject or the LAR. Consent will be obtained and documented in accordance with the regulations found at 45 CFR 46.111(a)(4), 21 CFR 56.111(a)(5), 45 CFR 46.111(a)(5), and 21 CFR 56.111(a)(5), as applicable.

DEFINITIONS

Legally Authorized Representative (LAR): an individual who is authorized under applicable law to grant permission on behalf of a potential subject for their participation in research.

Minimal risk: means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Qualified Practitioner: A physician assistant, certified registered nurse practitioner, certified nurse midwife, registered nurse authorized to perform a procedure delegated by a physician, a certified registered nurse anesthetist, another licensed physician other than the primary surgeon/practitioner, a resident, or a fellow. The Qualified Practitioner will have knowledge of the subject's condition and the procedure to be conducted on the subject and shall be acting under the supervision, at the direction of, or in collaboration or cooperation with the primary surgeon/practitioner.

PROCEDURES

A. General Requirements for Informed Consent. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. Informed consent must present information in sufficient detail relating to the research and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate. No informed consent may include

any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

B. Basic Elements of Informed Consent. The following information must be provided to each subject or LAR:

1. A statement that the study involves research, an explanation of the purposes of the research 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,

2. A description of any reasonably foreseeable risks or discomforts to the subject,

3. A description of any benefits to the subject or to others that may reasonably be expected from the research,

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject,

5. A statement describing the extent if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility the FDA may inspect the records if FDA regulated products are involved. For all studies, indicate that Office of Human Research Protection (OHRP) or other regulatory agencies may inspect records as required by law,

6. 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,

7. 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. This should include contact information for the research team for questions, concerns, or complaints and contact information for someone independent of the research team for any problems, concerns, and questions,

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled, and

9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

    i. 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

ii. 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.

C. Additional Elements of Informed Consent. When appropriate, one or more of the following elements of information shall also be provided to each subject or LAR:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable,

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the LAR's consent,

3. Any additional costs to the subject that may result from participation in the research,

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject,

5. A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject,

6. The approximate number of subjects involved in the study,

7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit,

8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions,

9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen),

10. The amount and schedule of all research-related payments to the subject, and

11. A conflict-of-interest disclosure statement.

D. Waiver or Alteration of Informed Consent. The IRB may waive the requirement to obtain informed consent or approve a consent process that does not include, or alters, some or all the required elements of informed consent if the IRB determines that:

1. <u>For general waiver or alteration of consent (including FDA-regulated research)</u>:
   a. the research involves no more than minimal risk to the subjects,
   b. the research could not practicably be carried out without the waiver or alteration,

c. 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,
d. the waiver or alteration will not adversely affect the rights and welfare of the subjects,
e. whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation, and

2. For research involving public benefit and service programs conducted by or subject to the approval of state or local officials:
   a. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
      i. Public benefit or service programs,
      ii. Procedures for obtaining benefits or services under those programs,
      iii. Possible changes in or alternatives to those programs or procedures; or
      iv. Possible changes in methods or levels of payment for benefits or services under those programs,
   b. The research cannot practicably be carried out without the waiver or alteration of informed consent.

3. For screening, recruiting, or determining eligibility. The IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:
   a. The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
   b. The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

* For Studies approved prior to 01/21/19:
Condition 1:
a. The research involves no more than minimal risk to the subjects,
b. The waiver or alteration will not adversely affect the rights and welfare of the subjects,
c. The research could not practicably be carried out without the waiver or alteration,
d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation, and
e. the research is not FDA-regulated.

Condition 2:
Subject to the approval of state or local government officials, research designed. to study, evaluate or otherwise examine public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs.

E. Documentation of Informed Consent. All subjects, or their LAR, must document that they are consenting to participate in any study that is conducted at MLH by signing and dating a written consent form, unless the IRB specifically waives the requirement for written

documentation of consent. The IRB may approve procedures for documentation of informed consent that involve:

1. A written consent document, approved by the IRB, that embodies the elements of informed consent set forth above. The form should be modeled according to the format in *MLH Informed Consent Guide*. This form may be read to the subject or the LAR, but, in any event, the person obtaining consent must give either the subject or the LAR adequate opportunity to read it before it is signed and dated. A written copy of the document must be given to the person signing the consent form.

2. A "short form" written consent document stating that the elements of informed consent set forth above have been presented orally to the subject or the LAR. When this method is used there must be a witness to the oral presentation. Also, the IRB must approve a written summary of what is to be said to the subject or the LAR. The short form consent document must be signed by the subject or LAR and the witness to the oral presentation. The written summary of the information that is presented orally must be signed by the person obtaining consent and the witness to the oral presentation. A copy of the short form consent document and written summary must be given to the subject or the LAR.

    a. When informed consent is documented using this short form procedure for non-English speaking subjects, the written summary should include all the elements of legally effective informed consent. The IRB-approved English language consent document may serve as the summary. The oral presentation (via Hospital translator services) and the short form written informed consent document should be in a language understandable to the subject or LAR. The witness should be fluent in both English and the language of the subject or LAR. The translator may act as the witness if present in person.

    b. The IRB will receive all foreign language versions of the short form as a condition of approval. Expedited review of these versions is acceptable if the protocol, the full English language informed consent document, and the English version of the short form document have already been approved by the IRB.

    c. If more than an occasional subject speaking the same non-English language will be enrolled in a study, then a fully translated consent form is required.

F. Waiver of Documentation. The IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it documents any of the following conditions apply:

1. For Research Not Regulated by the FDA, that the only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject (or LAR) will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern,
2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context, or
3. If the subjects or LAR are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

* For Studies Approved prior to 01/21/19:
  Condition 1:
  a. the research presents no more than minimal risk of harm to the subjects,
  b. the research involves no procedures for which written consent is normally required outside of the research context,
  c. the oral or written information provided to subjects includes all required and appropriate additional elements of consent disclosure, and
  d. the IRB has determined whether the participant should be provided written information.

  Condition 2:
  a. the only record linking the subject and the research would be the consent document,
  b. the principal risk would be potential harm resulting from a breach of confidentiality,
  c. each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern,
  d. the research is not FDA-regulated.
  e. the oral or written information provided to participants includes all required and appropriate additional elements of consent disclosure, and
  f. the IRB has determined whether the participant should be provided written information.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects or legally authorized representatives with a written statement regarding the research.

G. Remote Consent Documentation. The IRB may approve a process that allows the informed consent document to be delivered by mail, facsimile, email, or other web-based platform to the subject or LAR. The IRB also may approve a process for consent via telephone, provided that the subject or the LAR can read the consent document as it is discussed. Additionally, the IRB may consider and approve a process that allows electronic signature of the consent form by the subject or the LAR. All other applicable conditions and waivers for documentation of informed consent must be met when using these procedures**.**

H. Responsibility for Obtaining Consent.

1. The ultimate responsibility for ensuring that consent is properly obtained rests with the investigator, even though study coordinators or staff may be involved in the consent process. The IRB may permit an individual who is not the investigator to obtain consent with appropriate justification. If the IRB permits delegation of the informed consent process, **the investigator should have a detailed plan for the supervision and training of staff, and oversight of the clinical investigation, including the informed consent process.** The personnel who are permitted to obtain consent for each type of study are outlined below:

   a. Minimal Risk Study Not Involving Drug, Device, or Surgical Procedure. The IRB may permit an individual who is not the investigator obtain consent with appropriate justification. The individual who will be obtaining informed consent must be identified by name or position. The study application should describe the training and qualification of the individual.

b. Study Involving Drug, Device, or Surgical Procedure. The investigator responsible for obtaining informed consent must be a licensed physician. However, in accordance with the Pennsylvania Medical Care Availability and Reduction of Error (MCare) Act, the IRB may permit the investigator to fulfill their duty to obtain informed consent by **delegating the task to a Qualified Practitioner**. In addition to being within his or her scope of practice, this individual **must have the appropriate expertise and credentials to perform this duty as determined by the IRB**. The individual obtaining informed consent should be knowledgeable about the clinical investigation and have the appropriate training and credentials to be able to address any questions or concerns the subject may have about the study and/or alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

2. Retention of Original Consent. Investigators are to retain signed consent documents as required by federal regulations and the *MLH Administrative Policy on Records Management (Retention and Destruction)*. (See 21CFR 312.62, 21 CFR 812.140 and 45 CFR 46.115).

3. Signatures. The person who conducted the informed consent discussion is required to sign and date the consent form along with the subject or legally authorized representative.

I. Responsibility of the IRB. The IRB shall:

1. Review the proposed informed consent form for completeness according to the *MLH Informed Consent Guide.*

2. Require that information provided to subjects as part of informed consent includes the elements of informed consent as set forth in Section B and C.

3. Require that the informed consent document provides the required information in readily understandable wording (lay language). The reading level of the informed consent document should be no higher than an 8th grade level.

4. Have the discretion to modify the above requirements on a per study basis.

Origination Date: 08/13/01
Revision Date: 12/06/24

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **XIII**

Subject: **PLANNED EMERGENCY RESEARCH**

POLICY

The Institutional Review Board (IRB) may approve an exception to the requirements for informed consent for research on life threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent from research subjects or their legally authorized representatives.

The purpose of this policy is to outline the additional protections required by the regulations for planned emergency research where the requirements for informed consent are waived.

DEFINITIONS

A. Planned Emergency Research: Research involving human subjects who are in need of emergency medical intervention, e.g., comparison of methods for providing cardiopulmonary resuscitation, but who cannot give informed consent because of their life-threatening medical conditions and who do not have an available legally authorized representative to provide consent.
B. Legally Authorized Representative (LAR): an individual who is authorized under applicable law to grant permission on behalf of a potential subject for their participation in research.
C. Family Member: Both the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS) define a “family member” as any one of the following legally competent persons: spouse; parents; children, including adopted children; brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

GENERAL INFORMATION

A. Persons with life-threatening conditions who cannot either provide informed consent or refuse research participation are considered to be a vulnerable population. The lack of subject autonomy and inability of subjects to provide informed consent require that additional protections are provided in the review, approval, and performance of this research.
B. Prior and continuing IRB reviews are required for planned emergency research. The IRB must approve both the research and the exception to the requirements for informed consent, i.e., waiver, by finding and documenting that the regulatory criteria described below are met.
C. To approve a waiver of informed consent for research conducted in emergency settings, a licensed physician who is a member, or consultant, of the IRB and who is not otherwise participating in the research must agree with the IRB’s determination that the criteria for consent waiver are met. Documentation of the physician’s

concurrence is also required for approval; therefore, IRB meeting minutes should specifically record the physician's vote when planned emergency research is reviewed.

D. Planned emergency research conducted in life-threatening situations must be differentiated from the "emergency use" of an investigational drug or biologic or unapproved medical device. The emergency use provision in FDA regulations allows for a single use of an investigational drug or biologic or unapproved medical device for a human subject in a life-threatening situation for which no standard acceptable treatment is available and when there is not sufficient time to obtain IRB approval. For more information about the requirements for emergency uses, see the MLH IRB Policy on Emergency Use of an Investigational Test Article (VIII).

IRB APPROVAL OF A STUDY WHICH INCLUDES AN EXCEPTION TO THE REQUIREMENTS FOR INFORMED CONSENT

A. The IRB may approve emergency research without requiring that informed consent is obtained from subjects or their LAR only if the IRB finds and documents that each of the following requirements has been met:
    1. The human subjects are in a life threatening situation.
        - Available treatments are unproven or unsatisfactory.
        - The relative risks and benefits of the proposed intervention are unknown or thought to be equivalent, or better, compared to standard therapy.
    2. The collection of valid scientific evidence, including evidence from randomized, placebo-controlled studies, is necessary to determine the safety and efficacy of the intervention
    3. Obtaining informed consent is not feasible because of all of the following:
        - The subjects will not be able to give their informed consent as a result of their medical condition(s)
        - The intervention under investigation must be administered before consent from the subjects' LAR is feasible.
        - There is no reasonable way to prospectively identify the individuals likely to become eligible for participation in the research.
    4. Participation in the research holds out the prospect of direct benefit to the subjects because of all of the following:
        - Subjects are facing a life-threatening situation that necessitates intervention.
        - Appropriate animal and other preclinical studies have been conducted and the information derived from those studies, and related evidence, supports the potential for the intervention to provide a direct benefit to the individual subjects.
        - Risks associated with the research are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, and what is known about the risks and benefits of the proposed intervention or activity.
    5. The research could not practicably be carried out without the IRB approval of a waiver of informed consent.
    6. The protocol defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact an LAR for each subject within that window of time and, if feasible, to asking the LAR for consent rather than proceeding without consent
        - Investigators will summarize efforts made to contact the LAR and provide this information to the IRB at the time of continuing review.
    7. The IRB has reviewed and approved an informed consent process and consent document.

- The approved informed consent procedures and consent document are to be used with subjects or their LAR when feasible.
- The IRB has approved procedures and information to be used when providing an opportunity for a family member to object to the subject's participation, as described below.

8. Additional protections of the rights and welfare of subjects will be provided, including at least:
   - Consultation, including consultation carried out by the IRB, where appropriate, with representatives of the communities in which the research will be conducted and from which the subjects will be drawn.
     - Examples: Holding a public meeting in the community from which the subjects will be drawn to discuss the research, conducting a telephone poll, establishing a separate panel of community members, including community consultants to the IRB and adding unaffiliated members to the IRB who are representative of the community
     - The IRB will consider community input when reviewing the research.
   - Prior to initiation of the research, public disclosure of plans for the research and its risks and expected benefits to the communities in which the research will be conducted and from which the subjects will be drawn.
   - Public disclosure of sufficient information following completion of the research to apprise the community and investigators of the study, including the demographic characteristics of the research population and its results.
   - Establishment of an independent data monitoring committee to exercise oversight of the research.
   - If obtaining informed consent is not feasible and an LAR is not reasonably available, the investigator has committed to attempting to contact within the therapeutic window the subject's family member who is not a LAR, if feasible, and asking whether he/she objects to the subject's participation in the research.
     - Only one family member must be consulted and agre, (or object, to the subject's participation in the research
     - If more than one family member is present and family members disagree, the family members must work out the disagreement to enroll the potential subject.
     - Investigators will summarize efforts made to contact family members and provide this information to the IRB at the time of continuing review.

   Note: If a subject is enrolled in the study with waived consent and the subject dies before an LAR or family member can be contacted, information about the study, as described below, is to be provided to the subject's LAR or family member if feasible.
9. A separate IND or IDE is obtained for use of the investigational drug, biologic or device to be studied in a population that includes subjects who are unable to consent.

B. The IRB will approve procedures to inform the subject, the LAR, if the subject remains incapacitated, or a family member, if the LAR is not reasonably available, of the following at the earliest feasible opportunity:
   - That the subject was included in the study
   - Details of the research and other information contained in the informed consent document.
   - That the subject's participation may be discontinued at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Note: If it is an LAR or family member that is told about the study and the subject's condition improves, the subject is also to be informed as soon as feasible.

C. If the IRB cannot approve the research either because the criteria described above are not met or because of relevant ethical concerns, documentation of the IRB's findings will be provided in writing to the investigator and sponsor within 30 days.

The IRB will document the criteria for waiving the requirement to obtain consent and the criteria for approval of planned emergency research in the meeting minutes.

Origination Date: 08/13/01
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. XIV

Subject: SIGNIFICANT RISK/NONSIGNIFICANT RISK (SR/NSR) DEVICE DETERMINATIONS BY THE IRB

POLICY

It is the policy of the MLH Institutional Review Board (IRB) that a determination of Significant Risk or Nonsignificant Risk for a medical device must be made, unless provided by the Food and Drug Administration (FDA), before a medical device study may be approved.

BACKGROUND

The Investigational Device Exemptions (IDE) regulation (21 CFR 812) describes three types of device studies, the first two of which are subject to the IDE regulations: significant risk (SR), nonsignificant risk (NSR), and exempt studies.

DEFINITIONS

1.) Significant Risk Device **-** Under 21 CFR 812.3(m), an SR device means an investigational device that:

- is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject,
- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject,
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject, or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2.) Nonsignificant Risk Device - An NSR device study is one that does not meet the definition for an SR device study.

*Note: *See the January 2006 list of commonly studied medical devices for examples that may be helpful in making SR and NSR determinations, at the following website: http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf*

3.) Exempt Studies - The following studies are exempt from the requirements of 21 CFR Part 812:

- The study does not involve a device that is defined as a medical device under federal regulations.

- The study only involves devices used within their FDA-approved indications.
- The device is an exempt diagnostic device because the sponsor has complied with all requirements in 21 CFR 809.10c relating to labeling for in vitro diagnostic procedures and the testing, and the device:
    - is not invasive,
    - does not require any invasive sampling procedures that present significant risk,
    - does not by design or intention introduce energy into a subject,
    - and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- The device, other than a transitional device, is a predicate device (e.g., in commercial distribution immediately before May 28, 1976) and is being used in accordance with its labeling in effect at that time.
- The device, other than a transitional device, has 510(k) clearance and is being used in accordance with the indications in its labeling.
- The device is: (1) undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution; and (2) the testing is not for the purpose of determining safety or efficacy and does not put subjects at risk.
- The device is a custom device, generally provided to one physician for use in an individual patient and is not being tested for safety and efficacy for commercial distribution.

Note: If an exempt study is being conducted to collect data to support either a clinical investigation or a marketing application, then the study must comply with 21 CFR Part 50 and 21 CFR Part 56. For device studies that are exempt from the IDE regulations, the IRB does not need to decide whether the device poses a significant risk or nonsignificant risk. However, IRB approval is still required to review and approve the study before the investigation may begin.

MAJOR DIFFERENCES BETWEEN SR AND NSR DEVICE STUDIES

The major differences between SR and NSR studies are in the IDE approval process and in the sponsor's record keeping and reporting requirements, as outlined below.

1. *Significant Risk (SR) Device Studies*
    - SR device studies must follow all the IDE regulations at 21 CFR 812.
    - SR device studies must have an IDE application approved by FDA before they may proceed.
2. *Nonsignificant Risk (NSR) Device Studies*
    - NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b), However, there is no need to make progress reports or final reports to FDA.
    - These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion.
    - NSR device studies do not have to have an IDE application approved by FDA.
    - Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA.

Note: An IRB's NSR determination is important because the IRB serves as the FDA's

surrogate for review, approval, and continuing review of the NSR device studies. A NSR device study may start at the institution after the IRB reviews and approves the study and without prior approval by FDA.

PROCEDURES

SPONSOR/INVESTIGATOR RESPONSIBILITIES

A sponsor or the sponsor investigator, for investigator-initiated studies, is responsible for making the initial risk determination. The risk determination should be included with a new protocol submission within the iMedRIS application. The following information should be provided to the IRB:

- If the sponsor or sponsor/investigator identifies a device as NSR, the sponsor must provide the IRB with an explanation of its determination and any other information that may help the IRB in evaluating the risk of the device. For example, the IRB would need the description/specifications of the device, why the device qualifies as a NSR device, and if available, reports of prior investigations with the device.
- If FDA has previously determined that the device is NSR documentation should be provided.
- For Significant Risk device studies, the sponsor must submit an IDE application to FDA and receive approval, and the device's IDE number must be documented in the IRB application.
- Based on the risk determination by the IRB, or FDA, the sponsor or sponsor investigator must comply with the appropriate regulatory and reporting requirements (see MAJOR DIFFERENCES BETWEEN SR AND NSR DEVICE STUDIES)

Note: If the FDA has already made the SR or NSR determination for the study prior to submission to the IRB, the FDA's determination is final.

IRB Procedures

Unless FDA has already made a risk determination for the device study, the IRB is required to review the sponsor's risk determination. If the FDA has already made the SR or NSR determination for the study, the FDA's determination is final.

If the FDA has not already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination. If the IRB does not agree with the sponsor's assessment it will request that the determination be modified. The IRB may require the investigator to submit to FDA to obtain a risk assessment.

The IRB will consider the following in determining whether a device study is SR or NSR: the justification for risk determination, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure will be considered SR.

The IRB will document its SR or NSR determination, accordingly, including the rationale/discussion in the meeting minutes regarding SR protocols.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XV

Subject: CONTINUING REVIEW PROCESS

POLICY

The Institutional Review Board (IRB) conducts continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year. Continuing review of an approved study by the IRB occurs as long as the research remains active for the collection or analysis of identifiable private information about subjects, or for long-term follow-up of subjects, even when the research is permanently closed to the enrollment of new subjects and all subjects have completed all research-related interventions. Note: Studies received after 01/21/19 and approved by expedited review under 45 CFR 46[10] do not require an annual continuing review. These studies require an annual check-in to update study status, personnel, training and conflict of interest.

PROCEDURE

INVESTIGATOR RESPONSIBILITIES

1.) *Investigators are responsible for maintaining active IRB approval for ongoing studies and must have a procedure to track the status of studies and identify when information must be provided to the IRB for continuing review.*

- Investigators are required to submit a request for continuing review at least 30 days prior to the expiration date.
- **Without active IRB approval, there can be no intervention, interaction or follow-up with enrolled research subjects.** All study activity including recruitment of new subjects, advertisement, screening, enrollment of new subjects, conducting the consent process, interventions and/or interactions with existing subjects, the collection of identifiable private information from existing subjects, and the analysis of existing identifiable private information, must stop. See the MLH IRB Policy on Expiration of IRB Approval and Final Report Process (XVI) for more information.

2.) *Investigators are responsible for ensuring that either a continuing review submission or final progress report is submitted to the IRB sufficiently far enough in advance to prevent the expiration of IRB approval regardless of whether or not they receive a reminder notice from the MLH IRB.*

- Continuing review reminder notices are sent out from ORP approximately 4-6 weeks in advance of the study expiration.

[10] FDA-regulated research requires annual continuing reviews.

3.) *Investigators are expected to provide the IRB with all relevant information regarding the conduct of the research.*

- The materials that are required to be submitted for review are located in the Requirements for IRB Submission – Continuing Review for an Ongoing Study, Full and Expedited, Sheet and includes the following:
  - ORP Continuing Review Submission Form via iMedRIS that contains a status report on the progress of the research from the previous year
  - Approved Informed Consent/Assent Form(s) and any proposed changes to forms
  - Research Protocol
  - Additional information as provided by the investigator or determined to be useful by ORP Staff
  - IRB Correspondence during previous year, alternatively, summary may be submitted
  - Relevant post approval reports including any unanticipated study related events and any monitoring reports that have not been previously submitted to the IRB.

IRB PROCEDURES

Depending on the status of the study, the request for continuing review will be reviewed at either a convened meeting of the IRB or by expedited procedure. Refer to the MLH IRB Policy on Convened IRB Review Process (VI) and the MLH IRB Policy on Expedited Process (VII) for more information.

During review, the IRB determines if the currently approved consent document is still accurate and complete and any significant new findings that arise from the review process and might relate to the subject's willingness to continue participation will be provided to the subjects. In order to ensure that the research is conducted in compliance with all state and federal regulations for the protection of human subjects, the IRB may require verification of information from sources other than the investigator.

The IRB conducts continuing review at intervals appropriate to the degree of risk, but not less than once per year as applicable. The period of IRB approval, whether annually or more frequently than annually, will be documented in the written minutes of the convened meeting or on the IRB Expedited Approval letter. The approval notification sent to the investigator will specify the date IRB approval will expire or deadline to submit an annual update.

INVESTIGATOR RESPONSE TO IRB FINDINGS

The investigator must address all IRB required revisions and requests. The investigator may appeal IRB required revisions to the protocol and/or consent form. All such appeals must be in writing and submitted to ORP for review by the Chair or the convened IRB when applicable. Any statement of disagreement should be accompanied by a written justification for the disagreement. If resolution is not possible between the Chair and the investigator, the controverted issues would be returned to the convened IRB.

The investigator must include a copy of any revised documents including protocol and consent form with their responses with all changes highlighted, using track-changes.

Origination Date: 08/13/01
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XVI

Subject: EXPIRATION OF IRB APPROVAL AND FINAL REPORT PROCESS

POLICY

Investigators are responsible for maintaining active Institutional Review Board (IRB) approval for ongoing studies. Without active IRB approval there can be no intervention, interaction or follow-up with enrolled research subjects and no new subjects may be enrolled.

PROCEDURES

Investigator Responsibilities

Investigators must have a procedure to track the status of studies and identify when information must be provided to the IRB for continuing review or study closure, final report, process.

- Investigators must submit a request for continuing review or a final report via iMedRIS prior to the study expiration date. The expiration date of IRB approval is the last date a protocol is approved and is located on the IRB approval letter. If research approval expires before the study is reapproved all research activities must stop including interactions and interventions on current research subjects.
- If the IRB has not reapproved the research prior to the approval expiration date the research expires automatically at the end of the day, i.e., 12:00 a.m. of the expiration date. All study activity including recruitment of new subjects, advertisement, screening, enrollment of new subjects, conducting the consent process, interventions and/or interactions with existing subjects, the collection of identifiable private information from existing subjects, and the analysis of existing identifiable private information, must stop.

Note: Under no circumstances may subjects be enrolled into expired research unless the activity meets the criteria for emergency use of a test article in a life threatening situation without prior IRB review. If the research is completed, the investigator is required to submit a final report.

IRB Procedures

Expiration Reminders

Expiration/continuing review reminder notices are sent out from Office of Research Protections (ORP) via iMedRIS notifications approximately 60, 30, 10 and 5 days in advance of the study expiration. The investigator must submit a continuing review submission to the IRB through iMedRIS with enough time to ensure continued IRB approval and to permit the IRB sufficient time to conduct a complete review before the study's expiration date. If an investigator does not intend to request a reapproval, then a final report is required to close the study.

Expiration Action Notices

If no action has been taken by the investigator, approximately five (5) business days prior to the study expiration, an email notification, first notice of expiration, from ORP is sent via iMedRIS to the investigator and clinical research coordinator indicating that the study will expire and no research may be conducted past the expiration date. ORP may also contact the investigator and instruct him/her to stop all research related to the protocol prior to the expiration date.

If a request for continuing review is not submitted with enough time prior to the expiration date for the IRB to review and approve the research, and the investigator believes that continued research participation, i.e., treatment, during a lapse in approval would be in the best interests of individual subjects, such as to avoid creating an overriding safety concern or ethical issue, the investigator must make a request in writing to the IRB. The investigator's written request must contain the following:

- a description of the study activity that the investigator wishes to continue until IRB approval has been reinstated, with a justification for why its continuation would be in the individual subject's best interest,
- the number of subjects currently enrolled and the number of subjects for whom continued research participation would be in the person's best interest,
- an explanation for why the investigator failed to complete the timely renewal of the protocol, and the plan to prevent such a recurrence.

If a response to the notice of expiration is not received from the investigator within the requested timeframe, or a request for continuing review or a final report is not received a notice is sent warning the investigator of the pending expiration of IRB approval.

When a response to the notification is not received within in advance of expiration, ORP will contact the investigator with an expiration notification and require confirmation in writing that no research is ongoing.

IRB Action

Interventional studies involving active treatment which have a lapse in approval are reviewed by the IRB Chair and ORP Director to determine if there are safety or ethical issues if research activities are stopped.

If the protocol approval lapses the IRB may require actions including reconsent of affected subjects for continued study participation, or documentation of written permission from the affected subjects for use of any research data collected during the period of approval lapse. The IRB may require the investigator submit a Protocol Deviation/Violation Report that will explain the circumstances of the approval lapse and the plan to prevent a future lapse.

For instances of repeated failures to provide requests for continuing reviews resulting in lapses of IRB approval refer to the MLH IRB Policy on Noncompliance (XX). Lapses in IRB approval are not considered by Office of Human Research Protection (OHRP) to be a suspension or termination of IRB approval.

Final Reports are generally reviewed by Expedited Procedure, refer to MLH IRB Policy on Expedited Review Process (VII). Continuing reviews may be reviewed by either Expedited Procedures or by Convened IRB, refer to the MLH IRB Policy on Convened IRB Review Process (VI). Refer to the MLH IRB Policy on Expedited Review Process (VII) for a description of the items which are eligible for Expedited Review.

Origination Date: 08/13/01
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XVII

Subject: MODIFICATIONS AND AMENDMENT PROCESS

POLICY
Investigators may not initiate any changes in research procedures or consent form(s) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to research subjects.

DEFINITIONS
Modification or Amendment - refers to any change to the protocol design, the informed consent document and/or procedures, or the advertisement/recruitment procedures, from that originally approved by the IRB, regardless of how minor. Examples of modifications that require IRB review include but are not limited to, changes in:

- Study personnel
- Advertising materials (flyers, radio spots, etc.)
- Research procedures
- Subject populations (e.g., inclusion or exclusion criteria)
- Location where research will be conducted
- Consent form (including translations)
- Recruitment/advertising procedures
- Study design or methods
- Study status such as discontinuation or completion of a study, including the premature completion of a study.

Minimal risk - means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

MODIFICATION AND AMENDMENT TYPES
Minor changes that pose no more than minimal risk to subjects will be reviewed on an expedited basis. Amendments involving more than minor changes or involving changes that pose more than minimal risk will be reviewed by the convened IRB at the next available IRB meeting.

Amendments or modifications which are considered to be minor generally include:

- Administrative/editorial changes
- Minor consent form changes

- Minor changes to recruitment procedures, recruitment materials or submission of new recruitment materials to be used in accordance with approved recruitment methods.
- Minor changes to study documents such as surveys, questionnaires or brochures
- New study documents to be distributed to or seen by subjects that are similar in substance to those previously approved.
- Changes in payment to subjects or the amount subjects are paid or compensated that are not significant enough to affect the risk/benefit ratio of the study.
- Changes in the number and volume of sample collections as long as they do not negatively alter the risk/benefit ratio of the study.
- Addition of or changes in study personnel
- Addition of a new study site, in many but not all cases

Amendments or modifications that may increase risk to subjects, or those requiring substantive changes to the informed consent document, generally include:

- Use of a new drug or change in dose that may increase risk.
- Addition of an invasive procedure
- Addition of vulnerable subjects as a study population
- Changes in the inclusion/exclusion criteria that may involve populations at greater risk.
- Identification of new potentially significant risks
- Collection of additional blood samples that exceed the limits permitted for expedited review.

PROCEDURES

Investigator Responsibilities

- Investigators must promptly notify the IRB in writing of any modification or amendment, including changes to the protocol design, the informed consent document and/or procedures, or the advertisement/recruitment letter, from that originally approved by the IRB, regardless of how minor.
- Investigators may not initiate any changes in research procedures or consent form(s) without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject. In such cases, the investigator must promptly report this to the IRB as Unanticipated Problem (refer to the MLH IRB Policy on Unanticipated Problems Involving Risks to Subjects or Others (XVIII) for additional information.) The IRB will determine whether each change was consistent with ensuring the subjects' welfare.
- Investigators are responsible for submitting any proposed changes to the IRB and obtaining written IRB approval prior to implementing changes. Investigators are expected to provide the IRB with all relevant information regarding the proposed changes. The materials which are required to be submitted are located in the *Requirements for IRB Submission – Amendments to an Ongoing Study* (Full and Expedited) Sheet and includes the following:
  - ORP Protocol Submission Form via iMedRIS
  - Description of Modifications
  - Modified Informed Consent/Assent/HIPAA Authorization Form(s) when applicable.
  - Modified Research Protocol when applicable
  - Modified or new study documents when applicable

- Additional relevant information and materials regarding the proposed changes

The materials which are required to be submitted for additions in study personnel are located in *Requirements for IRB Submission – Addition of Research Personnel to an Ongoing Study* Sheet

IRB Review
Minor changes that pose no more than minimal risk to subjects will be reviewed on an expedited basis. Refer to the MLH IRB Policy on Expedited Review Process (VII) for more information. When subject reconsent is required the approval notification sent to the investigator by the IRB will specify when it is necessary for subjects to re-consent.

Amendments involving more than minor changes or involving changes that pose more than minimal risk will be reviewed by the convened IRB, at the next available IRB meeting. Refer to the MLH IRB Policy on Convened IRB Review Process (VI) for more information. The IRB will determine and document in the Minutes of the convened IRB when it is necessary for current subjects to re-consent to participation. The approval notification sent to the investigator will document when it is necessary for subjects to re-consent.

Approval Dates
For modifications and amendments to approved research, when no modifications are required to secure approval, the approval date is the date the research is approved at the convened IRB or the date the expedited letter is signed. When conditions/modifications are required to secure approval the date the modifications/conditions are met by the investigator becomes the effective date of IRB approval.

Investigator Response to IRB Findings

The investigator must address all IRB required revisions and requests. The investigator may appeal IRB required revisions to the protocol and/or consent form. All such appeals must be in writing and submitted to ORP for review by the Chair or the convened IRB when applicable. Any statement of disagreement should be accompanied by a written justification for the disagreement. If resolution is not possible between the Chair and the investigator, the controverted issues would be returned to the convened IRB.

The investigator is required to submit copies of any revised documents including protocol and consent form with their responses with all changes highlighted using track-changes.

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Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XVIII**

Subject: **Unanticipated Problems Involving Risks to Subjects or Others**

POLICY

Investigators are required to promptly submit written reports of events to the IRB that represent unanticipated problems involving risks to subjects and others.

PUPOSE

The purpose of this policy is to ensure events that may represent unanticipated problems involving risks to subjects or others, including unexpected and related adverse events are promptly reported to the Main Line Hospitals Institutional Review Board (MLH IRB) in accordance with regulatory requirements of the Department of Health and Human Services (DHHS) (45 CFR 46.103 (b) (5)) and the Food and Drug Administration (FDA) (21 CFR 56.108(b) (1)).

DEFINITIONS

1. Unanticipated Problems (UP): Unanticipated problems involving risks to subjects or others are defined as any incident, experience or outcome that meets all of the following criteria:

a) Unexpected (in terms of nature, severity, or frequency) given the research procedures and the subject population being studied, **and**
b) Related or possibly related to a subject's participation in the research, **and**
c) 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 and involves new or increased risk which requires some action, e.g., modification of the consent process or informing research subjects.

NOTE: "Possibly related" means that there is a reasonable possibility that the event may have been caused by the procedures/drugs/devices involved in the research.

2. Adverse event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, for example, abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with the subject's participation in the research whether or not considered related to the subject's participation in the research.

3. Serious Adverse Event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death
- A life-threatening event, places the subject at immediate risk of death from the event as it occurred
- requires inpatient hospitalization or prolongation of an existing hospitalization
- results in a persistent or significant disability/incapacity
- results in a congenital anomaly or birth defect, or
- any other adverse event that based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes in this definition.

4. Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5. Internal Event: An event that occurs at a study site under the jurisdiction of the MLH IRB.

6. External Event: An event that occurs at a study site that is not under the jurisdiction of the MLH IRB.

Reportable Problems/Events

Investigators are responsible for reporting events that meet the definition of an unanticipated problem, as defined above, to the IRB, which include adverse events which are unexpected, related and serious. An adverse event, or serious adverse event, may be expected, based on the known risks of the study and information in the informed consent and other study related documents. An adverse event is reportable only if it is also an unanticipated problem. In addition, unanticipated problems, even if not involving physical risks, need to be reported. Events should be reported regardless of whether they occur during the study, after study completion, or after subject withdrawal or completion:

Prompt reporting of the following unanticipated problems or events is required:

1. Internal adverse events that are unexpected, related to the research, and involve new or increased risks to subjects or others.
2. External adverse events that have been determined to be unanticipated problems involving risks to subjects or others.
3. Event including adverse event reports, injuries, side effects, breaches of confidentiality, or other problems occurring to subjects enrolled at this site or other sites in the same study, that occurs any time during or after the research study, which in the opinion of the principal investigator:
   - Involved harm to one or more subjects or others, or placed one or more subjects or other at increased risk of harm, **and**
   - Is unexpected, an event is unexpected when it is not described with specificity in the protocol, informed consent and other study related documents, or if described with specificity, it occurs beyond the expected frequency and/or severity, **and**
   - Is related to the research procedures, an event is related to the research procedures if in the opinion of the principal investigator it was at least possibly caused by the research procedures.

4. Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits, risk/benefit ratio, of the research. For example:
   - An interim analysis indicates that subjects have a lower rate of response to treatment than initially expected,
   - Safety monitoring indicates a particular side effect is more severe or more frequent than initially expected,
   - A paper is published from another study and shows an arm of the research study is of no therapeutic value.
5. A single occurrence of a serious adverse event that is unexpected and that is commonly and strongly associated with drug exposure, such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome.
6. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure but are otherwise uncommon in the study population, e.g., tendon rupture, progressive multifocal leukoencephalopathy.
7. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
8. Any change made to the research without prior IRB review necessary to eliminate an apparent immediate harm to research subject(s). The IRB will determine whether each change was consistent with ensuring the subjects' welfare.
9. Incarceration of a subject in a protocol not approved to enroll prisoners and the investigator considers it in the subject's best interest to remain in the study.
10. Any event that requires prompt reporting according to the research protocol or plan or the sponsor.
11. Any complaint of a subject when the complaint indicates an unanticipated risk or that cannot be resolved by the research staff.
12. Any accidental or unintentional change to the IRB approved research protocol or plan that involved risks or has the potential to recur, e.g., protocol violation.
13. An unanticipated adverse device effect. Any serious adverse effect on the health or safety, or any life-threatening problem associated with an investigational device.

Timeframe for Reporting

1. Events that may require a temporary or permanent interruption of study activities by the investigator or sponsor to avoid potential harm to subjects should be reported to the IRB immediately if possible, followed by a written report to the IRB using the appropriate reporting form for Unanticipated Problems via iMedRIS no more than five (5) working days after the investigator becomes aware of the event.
2. Internal Events should be reported to the IRB using the appropriate reporting form for Unanticipated Problems via iMedRIS within ten (10) working days of the investigator becoming aware of the event.
3. External Events should be reported to the IRB using the appropriate reporting form for Unanticipated Problems via iMedRIS within ten (10) working days of the MLH investigator becoming aware of the event ONLY IF either of the following are true:
   a. The MLH investigator has concluded that an immediate change to the protocol is necessary to address the risks raised by the event, OR
   b. A monitoring entity (e.g., an external IRB at the site where the problem or event occurred, the sponsor, or the Data Safety Monitoring Board) has required modifications/amendments to the research protocol or consent documents as a result of the event.

All reports should be submitted as soon as possible after the investigator learns of the

event but in all cases within ten (10) working days. For all reports, the following information should be included:

- Appropriate Reporting for Unanticipated Problems:
  - via iMedRIS for events which are Serious Adverse Events or Unanticipated Adverse Device Effects AND
  - via iMedRIS for all other events
  - The submission via iMedRIS should contain:
    - A description of any changes to be made to the conduct of the study and any corrective actions to be taken by the investigator.
    - A clear explanation of why the event or series of events has been determined to meet the criteria for reporting.
- Any additional information which may be useful for reviewing the event
- Approved Informed Consent/Assent Form(s)
- Current version of Research Protocol
- Additional information as provided by investigator.

4. At the time of continuing review, investigators should submit any unanticipated study-related events that have not been reported. If the study is subject to oversight by a monitoring committee, any monitoring reports which have not been previously submitted to the IRB should be included. These items should be identified on the Continuing Review submission via iMedRIS.

PROCEDURES

Investigator Responsibilities

It is the investigator's responsibility to analyze and review all AEs, SAEs and UPs that occur to determine if an event is reportable as an UP or UADE and determine the appropriate action to be taken in response.

At the time of Occurrence of a possible Unanticipated Problem:

The investigator reports problems under this policy by completing and submitting the appropriate Unanticipated Problems Report via iMedRIS for events which are Serious Adverse Events or Unanticipated Adverse Device Effects and via iMedRIS for all other events to the Office of Research Protections (ORP).

At the time of Continuing Review of a Protocol:

At the time of continuing review the investigator will report any unanticipated study related events that have not been previously reported on the Continuing Review Form viva iMedRIS.

IRB Procedures

ORP will review the submission to determine if sufficient information is provided and will make an initial assessment confirming that the event represents a possible unanticipated problem involving risks to subjects or others before referring them to the IRB Chair, ORP Director or their designee(s). If it is determined through clarification with the investigator that a report does not meet the requirements for reporting and is not relevant to the protection of research subjects, the report will be returned. The investigator will be notified by ORP Staff and educated regarding the requirements.

Reports of events determined during screening to represent a possible unanticipated problem involving risks to subjects or others will be sent to the convened IRB for review.

In the rare instance that the ORP Director and IRB Chair, or in their absence their designee(s), jointly determine that an immediate and life-threatening hazard exists for all

subjects enrolled in the study, the IRB Chair, or Vice-Chair, shall suspend the study immediately until the matter can be considered by a convened IRB subcommittee in accordance with SOP XXIV.

The convened board will review events that are a possible unanticipated problem as defined in this policy. All members of the convened IRB receive the appropriate reporting form for Unanticipated Problems as reported in iMedRIS including, the currently approved consent form, protocol, or protocol synopsis, and any supplemental information deemed relevant by the ORP and the IRB Chair to conduct a thorough review. Refer to the MLH IRB Policy on Convened IRB Review Process (VI) for more information. Based on the nature of the event and the expertise required to assess it the IRB Chair or designee(s) acts as the primary reviewer and presents findings to the convened IRB. No IRB member or consultant may participate in the review of any unanticipated problems in which the member has a conflict of interest except to provide information as requested.

At the time of continuing review, the IRB will review any unanticipated study-related events identified on the Continuing Review Form within iMedRIS that have not been previously reported and any monitoring reports which have not been previously submitted to the IRB. Refer to the MLH IRB Policy on Continuing Review Process (XV) for more information. Depending on the status of the study, the request for continuing review will be reviewed at either a convened meeting of the IRB or by expedited procedure. Refer to the MLH IRB Policy on Convened IRB Review Process (VI) and the MLH IRB Policy on Expedited Review Process (VII) for more information.

IRB Actions

The IRB will determine by convened IRB review whether the event is an Unanticipated Problem Involving Risks to Subjects or Others and if further action is necessary. Action(s) will be based on the nature of the event, degree to which research subjects or others are placed at risk, occurrence of previous problems, etc. The IRB will consider the rights and welfare of subjects or others when suspending, terminating, or modifying research.

The types of actions that the IRB may consider for any event include, but are not limited to:

- Modification(s) of the research protocol or procedures,
- Modification(s) of the consent process or consent form or information disclosed during the consent process,
- Providing additional information to current research subjects, required when such information may relate to their willingness to continue participation in the research,
- Providing additional information to past research subjects,
- Requiring current subjects to reconsent to participate,
- Requiring additional follow-up/monitoring for current and/or past research subjects,
- Monitoring of the research including audits or consent process,
- Education or mentoring for the investigator, sub-investigators and/or research staff,
- Modification of the continuing review schedule or additional reporting,
- Placing limitations on the investigator's research activities or use of research data,
- Suspending or terminating the research,
- Referral to other organizational entities or appropriate review process, e.g., noncompliance, medical peer review.
- For changes implemented without prior IRB review to eliminate an apparent immediate hazard to research subject(s) the IRB will consider whether each change was consistent with ensuring the subjects' welfare.

The IRB's determination and action(s), including votes taken, will be recorded in the meeting minutes. The requirements for quorum and majority apply. PIs will be notified in

writing of the IRB determinations and actions after IRB review.

Reporting of Unanticipated Problems Involving Risks to Subjects or Others
If the IRB determines that an event is an Unanticipated Problem Involving Risks to Subjects or Others, or if the Board suspends or terminates approval of research that is associated with unexpected serious harm to subjects or others, the investigator will be notified of the reasons for the IRB's action in writing.

The MLH IRB and Institutional Official (IO) will report through ORP unanticipated problems involving risks to subjects or others, terminations or suspensions of IRB approval as required by Federal regulations and MLH IRB Policy. Reports will be made to the Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) as applicable for FDA-regulated research, any sponsoring Federal Department or Agency or other sponsoring organization as applicable in accordance with MLH Federalwide Assurance. The IO, or his/her designee, will report to the appropriate Main Line Health Committee(s) as required. Notifications will be made within 30 days of the determination. See the MLH IRB Policy on IRB Reporting of Unanticipated Problems Involving Risks to Subjects or Others, Terminations or Suspensions of IRB Approval and Serious or Continuing Non-Compliance (XIX) for more information.

If the IRB does not consider the event to represent an unanticipated problem involving risks to subjects or others, no further action needs to be taken.

Principal Investigators with other regulatory, e.g., FDA, or contractual reporting requirements related to adverse events or Unanticipated Problems Involving Risks to Subjects or Others, e.g., the National Institutes of Health (NIH) and study sponsors, are responsible for providing any reports required under those regulations/agreements.

Origination Date: 06/20/02
Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **XIX**

Subject: **IRB Reporting of Unanticipated Problems Involving Risks to Subjects or Others, Terminations or Suspensions of IRB Approval and Serious or Continuing Non-Compliance**

POLICY

For all nonexempt human research that is federally funded or regulated by the U.S. Food and Drug Administration (FDA), regulations require that institutions and Institutional Review Board (IRBs) promptly report the following determinations to the investigator, Institutional Official (IO), and appropriate federal agencies:

- Unanticipated problems involving risks to subjects or others (See MLH IRB Policy XVIII)
- Serious or continuing noncompliance (See MLH IRB Policy XX)
- Suspensions of IRB approval (See MLH IRB Policy XXI)
- Terminations of IRB approval (See MLH IRB Policy XXI)

For all other research involving human subjects reports of these determinations are made to investigators, the IRB, and appropriate institutional officials.

The reporting requirements in this policy are not necessarily applicable to lapses in IRB approval. Lapses in IRB approval are not considered by Office of Human Research Protections (OHRP) to be a suspension or termination of IRB approval.

Report Content and Review

The Main Line Hospitals IRB (MLH IRB) and IO will report through the Office of Research Protections (ORP) unanticipated problems involving risks to subjects or others, terminations or suspensions of IRB approval and serious non-compliance or continuing non-compliance as required by Federal regulations and MLH IRB Policy. Reports will be made to OHRP, Food and Drug Administration (FDA), any sponsoring Federal Department or Agency or other sponsoring organization as applicable. The IO, or his/her designee, will report the serious or continuing non-compliance to the appropriate Main Line Health Committee(s).

A. Reports of IRB actions/determinations are initially drafted by the ORP Director or designee with assistance from the Main Line Health Legal Department or MLH Compliance Office.
B. Each report includes, but is not limited to, the following information:
    - The name of Institution and applicable identifying numbers, e.g., Federalwide Assurance Number
    - The name of the investigator
    - Name of the protocol and number

- The nature of the event
- The findings of the Organization
- Actions taken by the Organization
- Reasons for the Organization's or IRB actions
- Plans for continued investigation or action

C. Approval of report
- Draft reports will be reviewed and approved by the IRB Chair, or designee, and MLH Legal before being sent to the IO for signature.

Report Distribution and Timing
Reports of unanticipated problems, serious and/or continuing noncompliance, suspensions, and terminations will be distributed within 30 days of IRB final determination as described below. In some instances, preliminary reports may be sent prior to the completion of an investigation, final IRB determination and/or corrective actions. In such cases one or more follow up reports and/or a final report will be made when a final IRB determination has been made.

ORP staff will distribute copies of the signed report with applicable attachments to the following as required by regulations:

- OHRP, for Department of Health and Human Services (DHHS) regulated research.
- FDA, for FDA regulated research, except as described below.
- Other federal agencies when the research is overseen by the agency and separate reporting is required.
- Other organizations such as sponsors or contract research organizations when appropriate.
- Other sites involved in research when appropriate.
- MLH IO
- Other Organizational Officials including MLH Legal, MLH Compliance, other MLH Management

Reports of events occurring at MLH made through other organizations and mechanisms to federal agencies do not require duplicate reporting by MLH, however, reports may be distributed internally to the MLH IO, MLH IRB, MLH Legal, MLH Compliance and other MLH Management as required.

Studies reviewed under an IRB Authorization agreement
In the case of human subjects research that falls under an IRB Authorization agreement the responsibility for reporting serious or continuing noncompliance and suspension or termination of previously approved research will be retained by MLH whenever possible and will be described in specific agreements including:

1. Determinations made by the National Cancer Institute Institutional Review Board (NCI CIRB) will be reported by the NCI CIRB to the U.S. Office for Human Research Protection (OHRP) and FDA as required for events occurring at MLH.
2. Determination made by other Central/external IRBs for FDA regulated research will be reported by the external IRB to FDA as required for events occurring at MLH.
3. Determinations made by other external IRBs for federally, Department of Health and

Human Services (DHHS)/National Institutes of Health (NIH), funded research will be reported to OHRP by MLH for events occurring at MLH.

4. Determinations made by other external IRBs will be reported according to the terms described in specific agreements for events occurring at MLH.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XX**

Subject: **NONCOMPLIANCE**

POLICY

All personnel involved in research that is conducted within the Main Line Health System (MLH) have a responsibility to comply with federal regulations and organizational policies and procedures governing the ethical conduct of human subjects research and the determinations of the Main Line Hospitals Institutional Review Board (MLH IRB). Non-compliance may be directly identified by the MLH IRB or alleged by any source. All personnel share in the responsibility for reporting incidences of non-compliance to ensure the protection of human subjects participating in research conducted within the MLH.

I. DEFINITIONS

a) Non-compliance refers to the failure to comply with federal, state or local laws or regulations or MLH IRB policies, procedures or requirements, governing research and the protection of human subjects.

b) Allegation of non-compliance is a report of non-compliance from any source that has yet to be determined to be true.

c) An incident/finding of non-compliance is non-compliance identified through means such as audit(s), sponsor monitoring, protocol deviation(s), unanticipated problem(s) involving risks to subjects or others, or through allegation(s) of non-compliance that is determined to be true. An incident/finding of non-compliance may be further categorized as serious non-compliance or minor non-compliance, does not meet the definitions of serious or continuing non-compliance.

d) Serious non-compliance is non-compliance that increases risks to subjects, adversely affects the rights and welfare of subjects, or adversely affects the scientific integrity of the study.

e) Continuing non-compliance is an ongoing pattern of non-compliance. Continuing non-compliance may be due to unwillingness to comply with, or lack of knowledge of, federal, state or local laws or regulations, or MLH IRB policies, procedures or requirements, governing clinical investigations and the protections of human research subjects. Examples of continuing non-compliance may include but are not limited to repeated failures to provide or review progress reports resulting in lapses of IRB approval, inadequate oversight of ongoing research, or failure to respond to or resolve previous allegations or findings of non-compliance. Continuing non-compliance may be further categorized as serious non-compliance.

II. PROCEDURE

A. Reporting Allegations of Non-Compliance

Reports of observed, suspected or apparent non-compliance in human subjects research may come from any source, internal or external to MLH including but not limited to, investigators, research staff, physicians, sponsors, subjects or persons not directly involved in the research.

Reports of non-compliance must contain enough detail to understand the nature of the allegation and determine if there is sufficient information and basis in fact to investigate. Reports are encouraged to be provided in writing but may also be provided verbally and may be anonymous or identified.

Reports of non-compliance may be made to the Office of Research Protections (ORP) Director, Chair of the MLH IRB, ORP, MLH Compliance Office, or anonymously through the MLH ComplyLine, the confidential hotline for reporting compliance concerns. Verbal reports will be received and documented by the recipient.

Allegations of non-compliance will remain confidential to the extent possible. Employees who report non-compliance in good faith are protected under the MLH Compliance Non-retaliation, Whistleblower Protections, Administrative Policy VII.D.

Results of audits or review of on-site research records conducted by the ORP and the MLH Compliance Office, sponsor-monitor reports, or protocol deviations which result in an incident/finding of non-compliance should be handled as identified in Section II.C.

B. Handling Allegations of Non-Compliance

All allegations of non-compliance are to be referred to the MLH Compliance Office. The Compliance Office in coordination with ORP and MLH IRB Chair will process all allegations of non-compliance. Allegations of non-compliance will remain confidential to the extent possible consistent with the need to conduct an adequate investigation. Allegations of non-compliance will follow the process outlined in the MLH Compliance: ComplyLine – Internal Handling of Calls Administrative Policy (VII.H) when applicable.

On a timely basis, to determine if the allegation has a basis in fact, the MLH Compliance Office will undertake preliminary investigatory actions including but not limited to: a.) conducting an investigation or interviewing the investigator and study staff, alone or in consultation with ORP, the MLH IRB Chair, or others as deemed appropriate; b.) appointing a sub-committee to investigate; c.) collecting and reviewing relevant documentation; d.) consulting with internal or external experts or other knowledgeable sources. The MLH Compliance Office will take reasonable steps to ensure that individuals involved in the investigation do not have a real or perceived conflict of interest.

If an allegation of non-compliance is determined to have a basis in fact, refer to Section II.C. If an allegation is not based in fact, no further action is taken under this policy. If an allegation cannot be investigated adequately, for example due to insufficient detail, the investigation will be suspended until additional information is provided or discontinued when no additional information can be obtained. Results of investigations will be documented. The investigation should be completed as expeditiously as possible.

C. Handling Incidents/Findings of Non-Compliance

Non-compliance may vary in nature, severity, and frequency. For allegations of non-compliance which are determined to have a basis in fact the incidents/findings of non-compliance are reviewed by ORP and MLH IRB Chair to make an initial assessment to determine if the report of non-compliance is minor in nature, does not meet the definitions of

serious or continuing non-compliance. If it is determined the non-compliance is neither serious nor continuing, i.e., minor in nature, then the process under Section II.D. is followed.

The IRB Chair or Vice-Chair in consultation with ORP will make an initial assessment as to whether the incident/finding or allegation of noncompliance is serious and/or continuing noncompliance. For those incidents/findings or allegations which are thought to be serious or continuing the matter is referred to the convened IRB. For those incidents which are of such a nature that the safety, rights and welfare of subjects are at immediate risk or hazard the IRB Chair or Vice-Chair in consultation with ORP will contact the investigator in order to establish an interim measure to be taken to protect subjects until such a time that a convened IRB can review the study. An example of such a measure is to close the study to new subject enrollment.

At a convened MLH IRB meeting, after sufficient information is available, the MLH IRB must determine if an incident/finding or non-compliance is serious non-compliance, or continuing non-compliance. If it is determined that non-compliance is serious or continuing non-compliance, then the process under Section II.E. is followed.

D. Handling Incidents/Findings of Non-Compliance which are Determined to be neither Serious nor Continuing, i.e., Minor. If it is determined by ORP and the MLH IRB Chair that the incident/finding of non-compliance was minor and once recognized, the research team took the necessary corrective actions, the investigator will be notified in writing that the actions have been accepted and no further action is required under this policy.

If it is determined by the ORP and the MLH IRB Chair that the incident/finding of non-compliance was minor but was not recognized and the research team did not take the necessary corrective actions, ORP and/or MLH IRB Chair will advise the investigator and research team of the event and the necessary corrective actions. Alternatively, the ORP and/or MLH IRB Chair may refer the matter to the convened IRB. In this case the process under Section II.E. may be followed or adapted as necessary.

Corrective actions may include, but are not limited to, the following:

- Additional training or supervision of the investigator and/or the research team,
- Require enrolled subjects to be re-consented or provided with additional study information,
- Modification of the continuing review schedule,
- Modification of the auditing schedule,
- Modification of the research protocol or site specific standard operating procedure.

Once corrective actions are determined and accepted the investigator will be notified in writing and no further action is required under this policy

E. Handling Incidents/Findings of Non-Compliance which <u>are</u> Serious or Continuing
The convened MLH IRB will review incident/findings of non-compliance which may possibly be serious or continuing in nature. The investigator will be notified in writing that the matter has been sent to the convened IRB for review. ORP will provide as much information as possible related to the incident/finding to all members attending a convened meeting. The information will include at a minimum the report of the incident/finding, the protocol or protocol synopsis, and the current approved informed consent form. The MLH IRB may also be provided with the investigator's Drug/Device Brochure, if applicable. and other pertinent documents including inquiry correspondence to and from investigator or to the appropriate person at the institution.

The MLH Compliance Office, ORP or IRB Chair will present a summary of the events to date to the MLH IRB and may propose an initial Corrective and Preventative Action (CAPA) plan to

remedy the non-compliance. No IRB member or consultant may participate in the review of noncompliance in which the member has a conflict of interest except to provide information as requested.

The MLH IRB is authorized to collect additional information using a variety of methods before making a determination about whether there is non-compliance and whether it is serious or continuing, including, but not limited to: 1.) auditing or reviewing on site research records to be conducted by or at the direction of ORP and or/ the MLH Compliance Office; 2.) appointing a sub-committee to conduct its own investigation; or 3.) consulting with internal or external experts and other knowledgeable sources.

When the MLH IRB determines there has been serious or continuing non-compliance the IRB will determine what actions must be taken, if any, to protect enrolled subjects. Corrective actions may include but are not limited to the following:

- Suspend the research,
- Terminate the research,
- Notify current subjects of findings when it may relate to subjects' willingness to participate in the research,
- Provide additional information to subjects who have completed participation in the research,
- Modify the study protocol, consent form or site specific standard operating procedure,
- Modify information disclosed during the consent process,
- Require current subjects to be re-consented,
- Modify the continuing review schedule,
- Modify the auditing schedule,
- Monitor the research activities,
- Monitor the consent process,
- Refer the matter to appropriate MLH Departments when applicable (MLH Legal, the MLH Institutional Official or MLH Compliance).

Determinations of serious or continuing non/compliance by the MLH IRB will be documented in the meeting minutes and the investigator and the Institutional Official (IO) will be notified in writing of the determinations of the MLH IRB through ORP. The written notice to the investigator will include a request for the investigator to acknowledge in writing the receipt of the written notice and agreement to comply with any applicable conditions described therein. The written letter to the investigator will be sent as expeditiously as possible after the MLH IRB's determination of serious or continuing non-compliance.

The IO, or his/her designee, will report the serious or continuing non-compliance to the appropriate Main Line Health Committee(s) and applicable Federal Agencies. Refer to the MLH IRB Policy on IRB Reporting of Unanticipated Problems Involving Risks to Subjects or Others, Terminations or Suspensions of IRB Approval and Serious or Continuing Non-Compliance (XIX) for more information.

References: DHHS Regulations 45 CFR 46.103(b)(5), 45 CFR 46.113; FDA Regulations 21 CFR 56.108(b), 21 CFR 56.113.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXI

Subject: SUSPENSIONS OR TERMINATIONS OF IRB APPROVAL OF RESEARCH

POLICY

The Organization authorizes the Main Line Hospitals IRB (MLH IRB) to suspend or terminate human subjects research studies at a convened IRB meeting. Suspension or termination represents actions by the IRB to temporarily or permanently withdraw approval for research that is not conducted in accordance with IRB requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator.

DEFINITIONS

1. Suspension of IRB approval is a directive of a convened IRB to temporarily stop either some or all previously approved research activities to ensure protection of the rights and welfare of study subjects or for non-compliance. The Organization authorizes the Institutional Official (IO), IRB Chair/Vice-Chair or Office of Research Protections (ORP) to suspend a human subjects research study on an urgent basis when an event occurs and, in their judgment, taking such action cannot wait until a convened IRB meeting in order to protect the rights and welfare of subjects. An action taken by the IO or an IRB Chair to suspend or terminate research will be reported to and reviewed at a convened IRB meeting.

   Suspension of IRB approval remains in effect until the IRB determines whether the research may recommence with or without modifications to the research or whether the research must be terminated. Suspended protocols remain open and require Continuing Review.

2. Termination of IRB approval is a directive of the convened IRB to permanently stop some or all activities in a previously approved research protocol. If all research activities are terminated the research no longer requires Continuing Review. Termination of protocols approved under Expedited Review must be made by the convened IRB.

Note: A decision by an investigator to voluntarily suspend or terminate some or all research activities being conducted under an IRB approved research protocol is not considered a suspension or termination of IRB approval.

PROCEDURES

The following procedures are followed when a Suspension of IRB Approval or Termination of IRB Approval.

1. Suspension or termination of approval shall be documented in a written notice to the investigator along with the reasons for the action.
2. At a convened IRB meeting the IRB will determine and inform the investigator of steps to be taken as a result of suspension or termination of the research. Steps could include:
    - Notifying currently enrolled subjects or formerly enrolled that the study has been terminated by a written communication approved by the IRB. In this case communication to subjects will explain the rationale for the action taken,
    - Withdrawing of subjects, considering the rights and welfare of those individuals before such a step is taken including transferring subjects to another investigator, making arrangements for clinical care outside the research and permitting continuation in research under independent monitoring.
    - Informing the subjects of any follow-up procedures permitted or required by the IRB for subject safety, or
    - Submitting reports to the IRB and the sponsor of any adverse events or outcomes that occurred during the period when suspension or termination occurred.
    - Requiring adverse events or outcomes to be reported to the IRB
3. An action taken on an urgent basis by the IO, IRB Chair/Vice-Chair or ORP Director to suspend or terminate research will be reported to and reviewed at a convened IRB meeting. Refer to the MLH IRB Policy on Convened IRB Review Process (VI) for more information.
4. Reports of suspension(s) and termination(s) of IRB approval must be reported promptly. For reporting procedures of suspensions and terminations of IRB approval, refer to the MLH IRB Policy on Reporting of Unanticipated Problems Involving Risks to Subjects or Others, Terminations or Suspensions of IRB Approval and Serious or Continuing Non-Compliance (XIX) for more information.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXII

Subject: INVESTIGATIONAL TEST ARTICLES

POLICY
The Main Line Hospitals Institutional Review Board (MLH IRB) conducts initial approval and ongoing monitoring of all research involving investigational or unlicensed test articles. All research involving a device requiring an Investigational Device Exemption (IDE) or drug or other test article requiring an Investigational New Drug (IND) application will receive initial review by the convened IRB. Continuing review of research involving test articles will be conducted by the convened IRB unless expedited review is appropriate. (Refer to Expedited Review Process).

DEFINITIONS
Test article - means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to Food and Drug Administration (FDA) regulation, including dietary supplements, radioactive or cold isotopes, endogenous compounds, live organisms, cosmetics.

Investigational test article - means (i) an unapproved test article, or (ii) an approved test article being studied in a formal research study for a new indication, route of administration, dosage level, subject population or other factor that significantly increases the risks, or decreases the acceptability of the risks, associated with the use of the product.

PROCEDURES
IRB Review
In reviewing the FDA status of the test article the IRB considers (i) whether an IND or IDE is required (ii) whether a valid IND or IDE exists, and (iii) if a device is involved, whether the device is a significant risk or non-significant risk device. FDA determinations are accepted by the IRB, IND, IDE, Exempt Determinations, etc., and no further determinations are made.

In sponsored research involving test articles, the IRB relies on the sponsor to assure that all FDA requirements for test article research, including the existence of a required IND or IDE, are met. An investigator who sponsors, i.e., sponsor investigator, his/her own test article research must assume all the responsibilities imposed on both the sponsor and investigator by FDA regulations.

If an investigator does not have a required IND or IDE, the IRB will notify the investigator in writing that an IND or IDE is required for the research to be approved for enrollment of subjects. If the investigator does not agree with the IRB's determination the investigator may appeal the decision. If necessary, the investigator will also be asked to provide written documentation from the FDA that an IND or IDE is not required. When an IND is submitted to

the FDA it goes into effect 30 days after the FDA has received the IND unless the sponsor receives earlier notice from the FDA.

A sponsor or sponsor-investigator is asked to confirm that an IND or IDE number is valid. Acceptable documentation to confirm the IND number includes: 1.) the number that has been imprinted on the sponsor's protocol; 2.) the IND number is noted in written correspondence from the sponsor or 3.) the IND number is noted in written correspondence from the FDA, required if the investigator holds the IDE/IND. Note: The Investigator's Brochure (IB) may not be used for this purpose.

IND/IDE Determination

If an IND or IDE number or exemption determination is not provided in the application the IRB applies the FDA regulations to determine whether an IND or IDE is required.

IND

When research involves the use of a drug other than a marketed drug in the course of medical practice, the IRB must determine if the drug has an IND or the research meets one of the FDA exemptions from the requirement to have an IND. According to 21 CFR 312.2(b) an IND is not required for clinical investigation of a drug product that is lawfully marketed when:

(1) All six conditions below are met

1. it 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,
2. it is not intended to support a significant change in the advertising for the product,
3. it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks, or decreases the acceptability of the risks, associated with the use of the drug product,
4. it is conducted in compliance with the requirements for IRB review [21 CFR part 56] and informed consent [21 CFR Part 50],
5. it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7], and
6. it does not intend to invoke 21 CFR 50.24 (exception to informed consent in emergency situations).

(2) Clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:

1. Blood grouping serum
2. Reagent blood cells
3. Anti-human globulin
4. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
5. The diagnostic test is shipped in compliance with 21 CFR 312.160

(3) Use of a placebo and the investigation does not otherwise require submission of an IND.

(4) A drug intended solely for tests in vitro or in laboratory research animals.

Research involving dietary supplements, e.g., vitamins, minerals, amino acids, botanicals, etc., meeting the definition under the Dietary Supplement Health and Education Act (DSHEA) used ONLY to evaluate effects on the structure or function of the body, e.g., fiber supplement effect on gastric motility.

Clinical investigations involving radioactive or cold isotopes, endogenous compounds, live organisms, cosmetics and conventional foods may require an IND. Refer to FDA Guidance Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND for more information: http://www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf

IDE

When research is conducted to determine the safety or effectiveness of a device the IRB must determine device has an IDE issued by FDA, the research meets the requirements of an abbreviated IDE or the device meets one of the FDA exempt categories.

The investigation of a device other than a significant risk device fulfills the requirements for an abbreviated IDE when:

1. The device is not a banned device,
2. The sponsor labeled the device in accordance with 21 CFR 812.5;
3. The sponsor will obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval,
4. The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived,
5. The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations,
6. The sponsor will maintain the records required under 21 CFR 812.140(b)(4) and (5) and make the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10),
7. The sponsor will ensure that participating investigators will maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7), and
8. The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices.

The investigations of the following categories of devices are exempted:

1. The study does not involve a device that is defined as a medical device under federal regulations.
2. The study only involves devices used within their FDA-approved indications.
3. The device is an exempt diagnostic device because the sponsor has complied with all requirements in 21 CFR 809.10c relating to labeling for in vitro diagnostic procedures and the testing, and the device:
    a. is not invasive,
    b. does not require any invasive sampling procedures that present significant risk,
    c. does not by design or intention introduce energy into a subject,
    d. and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
4. The device, other than a transitional device, is a predicate device (e.g., in commercial distribution immediately before May 28, 1976) and is being used in accordance with its labeling in effect at that time.
5. The device, other than a transitional device, has 510(k) clearance and is being used in accordance with the indications in its labeling.
6. The device is: (1) undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution; and (2) the testing is not for the purpose of determining safety or efficacy and does not put subjects at risk.

7. The device is a custom device, generally provided to one physician for use in an individual patient and is not being tested for safety and efficacy for commercial distribution.

An IDE is required for significant risk device studies. Refer to the MLH IRB Policy on Significant Risk/Nonsignificant Risk Device Determinations by the IRB (XIV) for procedures for determining and distinguishing between a significant risk or non-significant risk device.

Investigator Responsibilities
An investigator must provide a list of all test articles and their regulatory status within the iMedRIS application. If no IND/IDE is provided an explanation regarding why no IND or IDE is required. If an unapproved medical device is involved and no IDE will be sought clarification as to whether the sponsor of the device considers the device to be a significant or non-significant risk device and the basis for that determination and supporting documentation when applicable.

NOTE: Any investigator who sponsors their own test article research assumes all the responsibilities imposed on both the sponsor and investigator by FDA regulations and all applicable MLH IRB policies and procedures.

Investigational test articles may only be used after research studies have been approved by the MLH Institutional Review Board (IRB) unless the test article is used in an emergency situation Refer to the MLH IRB Policy on Emergency Use of an Investigational Test Article VIII). Records of receipt, shipping documents, disposition, destruction and/or return must be kept as required.

Investigational drugs, biologics, devices or other test articles that are under the control of principal investigators which are used at Main Line Health must be procured, stored, secured, dispensed, used and monitored in accordance with all applicable policies and federal and state regulations.

Refer to the Investigations Drug Policy (3.80) in Pharmacy Department Policy and Procedure Manual for use of Investigational drugs or biologics which are administered and maintained by the MLH pharmacy department. Investigational drugs or biologics for research may be stored in appropriate areas in another facility other than the Pharmacy under the direct supervision of the investigator and in accordance with the sponsor, if applicable.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XXIII**
Subject: **HIPAA-Use of Protected Health Information (PHI) FOR RESEARCH**

Policy Purpose

The purpose of this policy is to establish guidelines for the use of Protected Health Information (PHI) and describe under what circumstances *PHI* belonging to Main Line Health, Main Line Hospitals, or other Main Line Health affiliated entity may be used for research[11] purposes.

POLICY

Protected health information belonging to Main Line Health (MLH), Main Line Hospitals, or other MLH Affiliate[12] may not be used internally or disclosed to any persons or organizations outside MLH for research purposes without prior approval by the Main Line Hospitals Institutional Review Board (MLH IRB) acting as the Privacy Board for research in accordance with this policy.

I. Definitions

1. Health Information (HI)[3] - means any information, including genetic information, whether oral or recorded in any form or medium that is created or received by a health care provider, health plan, public health authority, health care clearinghouse and relates to the past, present, or future physical or mental health condition of an individual, the provision of health care to an individual or the payment for provision of health care to an individual.
2. Individually Identifiable Health Information[3] - is a subset of HI, including demographic information collected from an individual and is created or received by a health care provider, health plan or health care clearinghouse that identifies the individual or for which there is a reasonable basis to believe the information can be used to identify the individual.
3. Protected Health Information (PHI)[13] **-** means individually identifiable health information.
4. Legally authorized representative - Legally Authorized Representative (LAR): an individual who is authorized under applicable law to grant permission on behalf of a potential subject for their participation in research.

[11] For the purposes of this policy, research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. (Refer to 45 CFR 164.501).
[12] MLH Affiliate is defined to be an entity of which Main Line Health, Inc. (or a Main Line Health subsidiary) is the parent organization.
[13] Complete definitions available at 45 CFR 160.103.

II. Access to PHI for Research[14]

The use and disclosure of PHI for research purposes may be authorized under the following limited circumstances[15]:

1. Preparatory to Research
2. Limited Data Sets with a Data Use Agreement
3. Subject Authorization for Research
4. Use/Disclosure with an Approved Waiver of Authorization
5. Research on Protected Health Information of Decedents
6. Accounting of Disclosures of PHI for Research

III. Procedures[16]

All requests for PHI for research purposes must be made and reviewed in accordance with the procedures explained below.[17]

1. **Reviews Preparatory to Research**

   The MLH IRB may allow the use and disclosure of PHI, *except* psychotherapy notes, to develop a research protocol or for similar purposes preparatory to research. This exception does not permit the continued use or disclosure of the PHI once the investigator has determined to go forward with the study.

   The MLH IRB may approve the use of PHI preparatory to research when the investigator certifies[18] to the following:

   1. Use or disclosure is sought solely to review PHI as necessary to prepare a research protocol or for similar purposes preparatory to research.
   2. No PHI may be removed from Main Line Health, Main Line Hospitals, or other MLH Affiliate by the investigator in the course of the review, and
   3. The PHI sought is necessary for the research purpose.

   During the preparatory review those granted access may only record HI in a form that is "de-identified." Investigators may not take any other notes or take away any PHI from the location where information is stored. **Appendix A** describes the information that must be removed to constitute de-identified *HI/PHI*.

   Limited information is available to investigators without MLH IRB approval. Statistical information such as the number and type of procedures performed, the number of patients assigned a particular diagnosis code and other data of a similar nature can be requested by an investigator as part of the work preparatory to developing a research proposal. To access such data the investigator must submit a request to Information Services.

2. **Limited Data Sets with a Data Use Agreement**

   MLH IRB may allow Main Line Health, Main Line Hospitals or other Main Line Health affiliated entity to use or disclose PHI contained in a "limited data set" for research purposes when use or disclosure is conducted as part of an IRB approved protocol as

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[14] Under the HIPAA rule, Business Associates Agreements are generally not required to share PHI with a researcher but may be employed as required by other MLH Policy.
[15] Special rules apply to the use and/or disclosure of psychotherapy notes for research purposes. (Refer to section III. Procedures).
[16] Any request involving *PHI* may require review by the Chief Privacy Officer for MLH.
[17] Users are prohibited under any circumstance to use personal electronic equipment to access MLH proprietary data or download PHI. Refer to Information Systems Policy: Personal Electronic Equipment
[18] Certification in not required for preparatory activities conducted by non-employee researchers on private medical records/charts (i.e. PHI which has not been collected, stored or maintained by Main Line Health, Main Line Hospitals, or other MLH Affiliate).

required. The recipient of the PHI must enter into a data use agreement through which the recipient Investigator agrees to protect the privacy of the data received and agrees to use the data in accordance with an IRB approved protocol.

A limited data set for research purposes excludes the following direct identifiers of the individual or of relatives, employers, or household members of the subject:

a. names
b. postal address information, other than town or city, state and zip code
c. telephone numbers
d. fax numbers
e. e-mail addresses
f. social security numbers
g. medical record numbers
h. health plan beneficiary numbers
i. account numbers
j. certificates or license numbers
k. vehicle identifiers and serial numbers including license plate numbers
l. device identifiers and serial numbers
m. web universal resource locators (URLs)
n. internet protocol (IP) address numbers
o. biometric identifiers, including finger and voice prints
p. full face photographic images and any comparable images

A data use agreement must:

a. establish that the recipient will only use and disclose the limited data set information for purposes of research, public health or health care operations
b. establish who is permitted to use or receive the limited data set
c. provide that the recipient will
    i. not use or disclose the limited data set information other than as permitted by the data use agreement or other applicable laws.
    ii. use the appropriate safeguards to prevent use or disclosure of the limited data set information other than as provided for by the data use agreement.
    iii. report to MLH IRB any use or disclosure of the limited data set information other than provided for in the data use agreement.
    iv. ensure that any agents including a subcontractor to whom the recipient provides the limited data set information agrees to the same restrictions and conditions that apply to the recipient.
    v. not identify the limited data set information or contact subjects.

A code or other means of record identification may be assigned to allow a limited data set to be re-identified provided that the code or other means of record identification is not derived from or related to information about the individual and is not otherwise capable of being translated as to identify an individual. The code cannot be used or disclosed for any purpose nor can the mechanism for re-identification be disclosed. Some data sets may be considered de-identified for the purpose of accounting of disclosures (see Section 6) and may be considered de-identified for research purposes (see Appendix B).

3. Subject Authorization for Research

PHI for research purposes may be used or disclosed in accordance with the terms of a valid authorization approved by the MLH IRB and signed by the research subject. Permissible uses and disclosures are limited to those described in the authorization. No one may be enrolled in any study without signing a research Authorization form.

The use and disclosure of psychotherapy notes for research is permissible only if the subject signs an authorization specifically authorizing the use of psychotherapy notes. Authorizations must include the following core elements:

a. description of PHI to be used or disclosed as part of the study.
b. who may use or disclosure the information.
c. who may receive the information.
d. purpose of each use or disclosure
e. expiration date
f. right to revoke authorization in writing and how to do it.
g. a statement that re-disclosures of PHI may no longer be protected.
h. signature of the subject and date, if the legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

An authorization may be a separate document or combined, except for psychotherapy notes, in an MLH IRB approved Informed Consent or any other type of written permission for the same or another research study and may be combined with an authorization for the creation or maintenance of a research database or repository. Psychotherapy notes require specific authorization and may not be combined with any other authorizations. A correction and/or an amendment of PHI in the conduct of research requires a new authorization to be approved by the MLH IRB and authorized by the research subject.

Compound authorizations which contain research related treatment conditioned on the provision of one of the authorizations must clearly differentiate between the conditioned and unconditioned[19] components and provide the individual with an opportunity to "opt in"[20] to the research activities described in the unconditioned authorization.

Authorizations for future research uses and disclosures are permitted when adequately described in the authorization such that it would be reasonable for subjects to expect that their PHI could be used or disclosed for such future research. The Authorization for future research must contain each of the core elements stated above and describe the purpose for the use and disclosure of PHI such that it would be reasonable for a subject to expect that PHI could be used or disclosed for future research purposes.

In the case of an LAR authorization may be obtained in person or when the LAR is unavailable in person by telephone or facsimile. When using telephone or facsimile the procedures outlined in the Main Line Health Administrative Policy on Informed Consent must be followed.

4. Use/Disclosure with an Approved Waiver of Authorization

The MLH IRB may grant an IRB approved waiver of authorization to allow the use and disclosure of PHI, except psychotherapy notes, for research purposes without subject authorization, when the investigator provides a description of the PHI to be used and requests a waiver as part of an IRB approved protocol. The MLH IRB must document that the requested waiver satisfies each of the following criteria:

[19] For example, an optional sub-study involving collection of additional blood/tissue samples for banking.
[20] A combined authorization that only allows the individual the option to "opt out" of the unconditioned research activities (e.g., ''check here if you do NOT want your data provided to the biospecimen bank'') is not permitted.

1. the use or disclosure involves no more than minimal risk to the privacy of the individuals because:
    - there is an adequate plan to protect the identifiers from improper use and disclosure
    - there is an adequate plan to destroy the identifiers at the earliest opportunity, unless there is a health or research justification for retaining the identifiers or their retention is required by law; and
    - there are adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except (1) as required by law, (2) for authorized oversight of the research project, or (3) for other research for which the use or disclosure of PHI is otherwise permissible under this policy.
2. the research could not practicably be conducted without the waiver; and
3. the research could not practicably be conducted without access to and use of the PHI. Note: If an investigator can practicably use de-identified health information or a limited data set for a research study, a waiver of authorization is not required and not subject to accounting of disclosures.

A waiver of individual authorization under this policy is not a waiver of the requirements of informed consent for participation in the study or of any other requirement in any other policy. Disclosures of *PHI* pursuant to a waiver must be tracked according to the requirements outlined in **Section III.6**.

5. Research on Protected Health Information of Decedents[21]

The MLH IRB may permit the use of PHI of decedents for research purposes without an authorization when the investigator certifies that:

1. the use or disclosure sought is solely for research on PHI of decedents, i.e., investigators may not request a decedent's medical history to obtain health information about a decedent's living relative,
2. documentation at the request of MLH IRB of the death of such individuals
3. the protected health information for which use or disclosure is sought is necessary for the research purposes.

6. Accounting of Disclosures of PHI for Research

The Privacy Rule gives individuals the right to receive an accounting of certain disclosures, not "uses", including research involving PHI that occurred during the six years prior to the individual's request for an accounting. Accounting of disclosures of PHI is required in 1) connection with a protocol for which the MLH IRB approved a waiver/alteration of authorization, 2) research on decedents' information and 3) reviews preparatory to research. The types of disclosures that are exempt from this accounting requirement are:

a. research disclosure made under an authorization.
b. research disclosures of limited data sets under a data use agreement
c. research disclosures of de-identified information
d. exempt research when information recorded cannot be identified, directly or through identifiers linked to subjects.

Research related *PHI* disclosures subject to accounting will follow the process outlined in the HIPAA – Patient's Right to Full Accounting of Disclosures MLH Administrative Policy (VII.11).

[21] PHI of a deceased individual is protected for a period of 50 years following the death of the individual.

When the records of 50 or fewer individuals are disclosed, the investigator is responsible for providing MLH Information Management with the following information:

a. date of disclosure
b. name of the recipient and address if known
c. brief description of the PHI disclosed
d. brief statement of the purpose of the disclosure that reasonably informs the individual of the basis for disclosure, or a copy of the request for the disclosure.

When more than 50 records of individuals are disclosed the investigator is responsible for providing Health Information Management with the following information:

a. the name of the protocol or other research activity,
b. a brief description of the research protocol or other research activity, including the purpose of the research and the criteria for selecting particular records,
c. a brief description of the type of PHI that was disclosed,
d. the date or period of time during which disclosures occurred,
e. the name, address and telephone number of the entity that sponsored the research and of the investigator to whom the information was disclosed, and
f. a statement that the PHI of the individual may or may not have been disclosed for a particular protocol or other research activity.

References: Health Insurance Portability and Accountability of 1996 Act (HIPAA), as amended 2013

Origination Date: 01/03
Revision Date: 12/01/23

Appendix A

De-Identified Health Information

Health information is de-identified when one of the following two conditions are met.

1. The following identifiers of the individual or of relatives, employers, or household members of the individual are removed:
   - Names
   - All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census:
     - the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
     - the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people are changed to 000.
   - All elements of dates, except year, directly relating to an individual, including birth date, admission date, discharge date, date of death and all ages over 89 and all elements of dates (including year) indicative of such age, except for ages and elements aggregated into a single category of age 90 or older.
   - Telephone numbers
   - Fax numbers
   - Email addresses
   - Social security numbers
   - Medical record numbers
   - Health plan beneficiary numbers
   - Account numbers
   - Certificate/license numbers
   - Vehicle identifiers and serial numbers, including license plate numbers
   - Device identifiers and serial numbers
   - Web Universal Resource Locators (URLs)
   - Internet Protocol (IP) address numbers
   - Biometric identifiers, including fingerprints and voice prints
   - Full face photographic images or any other comparable images
   - Any other unique identifying numbers, characteristics or codes, other than unique codes assigned to code the data.

   Note that any codes used to replace identifiers in data sets cannot be derived from any information relating to the individual and the master codes, nor can the method to derive the codes be disclosed.

   Although the use of codes is recommended as a means of reducing risk, if an investigator has the ability to link coded data to identifiable information the coded data will be considered to be identifiable, i.e., PHI or individually identifiable health information. Only when the investigator has no access to the de-identified information, the coded data will be considered de-identified and not *PHI* or individually identifiable health information.

2. A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, de-identified, determines that the risk is very small that the information could be used alone or in combination with other reasonable available

information by an anticipated recipient to identify a subject and documents the methods and results of the analysis that justify the determination.

Appendix B

De-Identified Data Review Requirements*

OHRP[22] considers private information[23] or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. For example, OHRP does not consider research involving **only** coded private information or specimens to involve human subjects as defined under 45 CFR 46.102(f) if the following conditions are both met:

a. the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and

b. the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

- the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased. Note that the HHS regulations do not require the IRB to review and approve this agreement.
- there is are IRB approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased,
  or
  there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.

This interpretation applies to existing private information and specimens, as well as to private information and specimens to be collected in the future for purposes other than the currently proposed research. The following are examples of private information or specimens that will be collected in the future for purposes other than the currently proposed research: (1) medical records; and (2) ongoing collection of specimens for a tissue repository.

*Current Food and Drug Administration (FDA) guidance indicates that IRB review is required for any In Vitro Device Study involving human specimens/samples, even when the specimens are leftover human specimens, the research involves no identifiers or the biological materials cannot be linked to any identifying information. (FDA regulations do not contain exceptions from the requirements of informed consent on the grounds that the specimens are not identifiable and or that they are remnants of human specimens collected for routine clinical care or analysis that would otherwise have been discarded. Nor do FDA regulations allow IRBs to decide whether or not to waive informed consent for research involving leftover or unidentifiable specimens). However, the FDA has indicated it may exercise enforcement discretion in certain situations. See 2006 FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable.

[22] Office of Human Research Protection which oversees the protection of human subjects in research. Complete guidance available at: http://www.hhs.gov/ohrp/policy/cdebiol.html

[23] Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXIV

Subject: DECISIONALLY IMPAIRED TO CONSENT AND SURROGATE CONSENT

PURPOSE

The purpose of this Policy is to provide Guidelines and procedures for the Main Line Hospitals Institutional Review Board (IRB) and investigators in proposing, conducting and reviewing research in subjects with impairments in cognition, decision making, and/or ability to communicate.

POLICY

It is the policy of the IRB, by and through its subcommittees, to protect a research subject's right to autonomy. It is also the IRB's policy to protect those with diminished autonomy or reduced capacity to consent to research or to provide authorization for the use and/or disclosure of their protected health information.

However, the IRB recognizes that substituted consent is necessary in order to offer experimental treatments to subjects incapable of making autonomous choices where the research poses more than minimal risk, but where the risks to the subject are reasonable in relationship to any anticipated benefits to subjects, and to the importance of the knowledge that may reasonably be expected to result from the research. Accordingly, the following procedures will be followed when the investigator determines that a patient is unable to give informed consent for participation in research and/or is unable to give a HIPAA Authorization.

DEFINITION

Legally Authorized Representative (LAR)- means an individual or judicial or other body authorized under applicable law to consent on behalf of a potential subject to the subject's participation in the procedure(s) involved in the research

BACKGROUND

A. Informed Consent

Federal regulations require that the investigator obtain the legally effective informed consent of the subject or the subject's LAR prior to medical research. Federal law defers to state law to determine what surrogate is legally authorized to substitute consent.

Pennsylvania law requires the informed consent of the subject or the subject's LAR before the administration of an experimental medication, the use of an experimental device, or the use of an approved medication or device in an experimental manner.

Pennsylvania law also authorizes substituted consent to the performance of an

experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral research by the subject's court-appointed guardian pursuant to a court order issued after fact finding. Finally, Pennsylvania statutory law further authorizes a person named in the subject's power of attorney for health care to consent to medical, therapeutic and surgical procedures.

While Pennsylvania statutory law does not explicitly authorize substituted consent in the absence of a power of attorney or court-appointed guardian, case law strongly supports substituted consent by close family members when patients lack capacity to make medical decisions. When the subject is unable to give informed consent, the subject's close family member or significant partner is in the best position to determine the wishes of the subject regarding participation in therapeutic research. (In re. Fiori, 543 Pa. 592, 673 A.2d 905 (1996)

PROCEDURES

I. Submission and Review of Protocols Involving Subjects with Diminished Functional Abilities or No Capacity to Provide Informed Consent

A. The investigator shall be responsible for making the determination as to whether the research protocol shall or shall not enroll subjects with diminished functional abilities or incapable of giving informed consent. This determination shall be specific for the protocol in question and not a general account of the individual's ability to consent. When feasible, the investigator should make efforts to support or enhance potential subjects' ability to consent by employing special measures such as repetition, including at later times in the study, multi-media presentation, interactive questioning, written study summaries, and conducting the consent process in an environment in which the subject is comfortable.

B. If it is anticipated that the research will involve individuals with diminished capacity to consent the protocol shall describe the process by which the investigator will determine and document the individual's ability to provide consent. The protocol shall also describe the process by which the investigator shall obtain assent/surrogate consent. Subjects with impairments in functional abilities are presumed to be capable of providing consent unless there is substantial evidence that they are not. The mere presence of a condition that leads to diminished functional abilities does not necessarily indicate lack of capacity to consent.

C. The IRB shall review such protocols and determine and document whether:

1. The risks to the subjects, recognizing that some physical and social risks may be heightened in individuals with conditions that may cause diminished functional abilities, are reasonable in relationship to any anticipated benefits to subjects and to the importance of the knowledge that may reasonably be expected to result, and
2. The population targeted for recruitment represents the population with the least degree of impairment to functional abilities compatible with the aims of the study, and
3. Appropriate procedures for assessing potential subjects' capacity to consent are described in the protocol. Note: the assessment methodology should increase in rigor as the degree of risk in the study and the extent of likely impairment to potential subjects' functional abilities

increase, and

4. the description of the informed consent process to be used is appropriate to the risk of the protocol as assigned by the IRB, and
5. The appropriateness of the assent/surrogate consent and consent process described in the protocol for obtaining informed consent, and
6. All other aspects of the proposed research as provided in the IRB Policy and Procedure Manual are appropriate.

D. If the IRB determines that the risk to the subject is greater than minimal risk it may require additional safeguards to ensure that the rights of such subjects are protected. Such additional protections that the IRB may consider may include, but are not limited to:

1. Independent advocate assessment of subjects' ability to assent, and/or surrogates ability to consent, for example, an independent advocate may be a physician unrelated to the protocol or subject's primary care physician, consistent with IRB policies and procedures.
2. The appropriateness of the individual serving as the personal representative/surrogate.
3. Other safeguards as appropriate.

E. The IRB shall not approve any research involving the use of surrogate consent if they determine that the risk to the subject outweighs the anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.

II. Determination of Subject's Ability to Provide Informed Consent in a Research Study

A. The investigator shall be responsible for determining whether an individual subject can provide informed consent.

B. The investigator will document in the research record the reason for the subject's inability to provide informed consent.

C. The investigator shall apply and document any additional safeguards as directed by the IRB.

III. Individuals Able to Provide Effective Surrogate Consent

For research conducted in the Commonwealth of Pennsylvania the following individuals may be considered an LAR of the subject and capable of providing surrogate consent:

1. A court appointed guardian authorized to consent to the subject's participation in the protocol in a current court order issued within the subject's jurisdiction.
2. A health care agent appointed by the subject in a power of attorney.
3. If neither of the above are designated the investigator may obtain the informed consent of the following individuals in the order listed below:
   a. Spouse, unless an action for divorce is pending, and the adult children of the subject who are not the children of the spouse.
   b. Adult child
   c. Parent
   d. Adult brother or sister
   e. Adult grandchild
   f. An adult individual with a significant personal relationship with the subject to warrant their authority. In situations as described in this subsection "f",

investigator should document the reasons why such relationship is considered to be significant.

For human subject research conducted in jurisdictions outside Pennsylvania the MLH Legal Department determines who meets the definition of LAR as defined by FDA and DHHS and resolves conflicts among applicable laws. The investigator or the IRB will contact MLH Senior Counsel to assist in determining who under local law may serve as a LAR.

IV. Responsibilities of the LAR in the Surrogate Consent Process

The surrogate should base his or her decision on the subject's expressed wishes, including an advanced directive, if available, or if unknown, what the subject would have desired in light of his or her prognosis, values, and beliefs. In the event of a disagreement among potential subject surrogates, an attempt to reach consensus shall be made through the intervention of a subject advocate appointed by the IRB if available. If consensus is not possible a court appointed guardian should be obtained before the subject is enrolled in the study. When a surrogate provides consent for a subject's participation in a research project it is preferable for that surrogate to remain the responsible party for all subsequent research decisions including but not limited to withdrawal of consent.

If there is reasonable concern that a surrogate is incapable or unwilling to execute his/her responsibilities, his/her consent shall not be sufficient to enroll the subject in the study.

Requirements for Subject Assent

If it is determined that a potential subject or subject's LAR cannot provide consent, the investigator should make reasonable efforts to determine if he/she can communicate his/her preferences regarding participation in the study or a component of the study, offer information regarding the procedures that he/she will undergo, and ensure that his/her participation is willing. This assent may be oral but should be documented. If a subject dissents repeatedly to participation in a study or component, he/she should be withdrawn from the study or component. If this is not feasible for medical or safety reasons, he/she should be kept on the study intervention under compassionate or off-label use if possible.

V. Requirement for Re-consent

A.If at any time after the subject is enrolled in a study through surrogate consent, he or she regains the capacity to provide informed consent the investigator shall obtain the legally effective informed consent of the subject for continued participation in the research.

IV. Documentation of LAR Consent

a. LAR – must sign the consent form under the section for "Legally Authorized Representative"
b. Witness – the signature of the patient surrogate decision maker must be witnessed by someone other than the responsible physician. The purpose of the witness is to verify the authenticity of the patient's surrogate decision maker's signature, not the adequacy of the consent.
c. Telephone/Facsimile Consent –may be obtained by telephone or facsimile only if the patient' surrogate decision maker is unavailable in person. Telephone consent may be obtained to prevent an unreasonable delay in patient care and should be witnessed by a hospital employee. The "Verbal Telephone Consent" section must be completed and signed by the person obtaining telephone consent and the witness to the telephone consent.

Note: Refer to the procedures outlined in the Main Line Health Administrative Policy on Informed Consent for additional information for documenting consent by the LAR.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XXV**
Subject: **RESEARCH INVOLVING PREGNANT WOMEN, NEONATES AND FETUSES (45 CFR 46 Subpart B)**

POLICY

For research involving pregnant women or human fetuses or neonates, the IRB will approve only research which satisfies the applicable conditions in accordance with 45 CFR Part 46 Subpart B. These additional safeguards to protect the rights and welfare of subjects when some or all of the subjects are pregnant women or fetuses, or neonates apply regardless of the source of funding. This policy also applies to research involving post-delivery placentas, dead fetuses, or fetal material.

DEFINITIONS

Dead fetus - means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery - means complete separation of the fetus from the woman by expulsion or extraction or any other means.

Fetus - means the product of conception from implantation until delivery.

Neonate - means a newborn.

Nonviable neonate - means a neonate after delivery that, although living, is not viable.

Pregnancy - encompasses the period of time from implantation until delivery. A woman will be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

Viable - as it pertains to the neonate, means being able, after delivery, to survive, given the benefit of available medical therapy, to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the Federal Register guidelines to assist in determining whether a neonate is viable for the purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements for Research Involving Children, refer to the MLH IRB Policy on Research Involving Children as Subjects (XXVII).

PROCEDURES

IRB Process

1. **For research involving pregnant women, fetuses, or neonates -** The IRB will approve the conduct of the research only if it finds that the research meets the regulatory criteria for approval addressed under the federal regulations at 45 CFR 46 Subpart B (45 CFR 46.204, "Research involving pregnant women or fetuses prior to

delivery"; 45 CFR 46.205, "Research involving neonates"; 45 CFR 46.206, "Research involving, after delivery, the placenta, the dead fetus, or fetal material").

2. **For research that does not meet the criteria for approval** – If the research does not meet the criteria for approval addressed under 45 CFR 46.204, "Research involving pregnant women or fetuses prior to delivery"; 45 CFR 46.205, "Research involving fetuses after delivery"; or 45 CFR 46.206, "Research involving, after delivery, the placenta, the dead fetus, or fetal material," the IRB must find that:
    - the research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses; and
        i. if the research is funded by the Department of Health and Human Services (DHHS), it will be submitted for review and approval by the Secretary, DHHS, in accordance with the provisions of 45 CFR 46.207, or
        ii. if the research is not federally supported, the IRB in consultation with MLH Legal counsel and with health care experts will consider on a case-by-case basis.

CONSENT REQUIREMENTS

1. Pregnant Women/Fetus Prior to Delivery

For research involving pregnant women or the fetus prior to delivery, the documented, written informed consent of the pregnant women or her legally authorized representative will be obtained in accordance with the provisions of 45 CFR 46.204; unless the IRB grants either a waiver of informed consent in accordance with 45 CFR 46.116(d) or a waiver of the requirement to document informed consent in accordance with 45 CFR 46.117(c).

2. Neonates of Uncertain Viability

For research involving neonates of uncertain viability, the documented, written informed consent of either parent or the legally authorized representative of either parent will be obtained in accordance with the provisions of 45 CFR 46.205; unless the IRB grants either a waiver of informed consent in accordance with 45 CFR 46.116(d) or a waiver of the requirement to document informed consent in accordance with 45 CFR 46.117(c).

3. Nonviable Neonates

For research involving nonviable neonates, i.e., neonates determined to be unable, after delivery, to survive to the point of independently maintaining heartbeat and respiration, the documented, written informed consent of both parents will be obtained in accordance with the provisions of 45 CFR 46.205.

- If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the IRB may approve the research based on the consent of one parent.

Note: the consent of the father need not be obtained if the pregnancy resulted from rape or incest.

Note: the IRB may not grant approval for legally authorized representative, i.e., surrogate, consent or a waiver of the requirement to obtain consent, i.e., 45 CFR 46.116 (c) or 45 CFR 46.116 (d), for research involving nonviable neonates.

4. Fetal Material Derived from Abortion

For research involving the dead fetus or fetal material derived from an induced abortion, the documented written informed consent of the mother must be obtained in accordance with the Pennsylvania Abortion Control Act.

- The research protocol must specify that informed consent for use of the fetal tissue for research will be obtained separately from, and after, the consent is obtained for the abortion.
- No remuneration, compensation or other consideration of any kind may be offered to a woman to consent to the use of fetal tissues for research.
- The donor may not designate the recipient of fetal tissue.
- All persons who participate in the procurement, use or transplantation of fetal tissue must be informed as to the source of the tissue, e.g., abortion, miscarriage, still birth, ectopic pregnancy. Any protocol that involves an intervention derived from fetal tissue must include the information as part of the informed consent document and/or process.
- Under Pennsylvania law any nontherapeutic medical procedure performed upon a fetus may be considered to be a third-degree felony. 18 Pa.Con.Stat Section 3216(a).
- If investigators are obtaining fetal tissues or organs from sources outside of MLH, confirmation must be provided from the outside source that the material was collected with appropriately obtained consent under applicable laws.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXVI

Subject: RESEARCH ACTIVITIES INVOLVING PRISONERS AS SUBJECTS (45 CFR 46 Subpart C)

POLICY

For research involving prisoners, the IRB will review and approve research involving prisoners under 45 CFR Part 46, Subpart C before research is initiated. These additional safeguards to protect the rights and welfare of subjects when some or all of the subjects are prisoners apply regardless of the source of funding.

DEFINITIONS

Prisoner - A prisoner is defined as "an individual involuntarily confined or detained in a penal institution" and encompasses individuals sentenced to such an institution under criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. **NOTE:** ***This definition includes any individual who enrolls in a research study and then becomes a prisoner while in the study*****.**

Prisoner Representative - An individual who is currently or formerly a prisoner or an individual who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner, e.g., prison chaplain, prison social worker, or prison health care worker.

Minimal Risk - For research involving prisoners, the IRB will use the following definition for "minimal risk": "Minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons (emphasis added)."

IRB REQUIREMEMTS

Research involving prisoners will be reviewed by the convened IRB review process which includes at least one member who is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity. This includes initial review, continuing review, full-board modifications, and reportable unexpected or unanticipated problems.

- Modifications that would otherwise be approvable by expedited review can be expedited as long as the prisoner representative receives a copy of the modification and concurs that it does not adversely affect the prisoners.

A. The IRB will approve the research only if it finds and documents that:
    1. the research meets one of the regulatory criteria for approval addressed under 45 CFR 46.306 (a)(2); that is the research is a study of:
        - the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
        - prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
        - conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or
        - practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.
    2. any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, and quality of food, amenities and opportunity for earnings in the prison, are not of such magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
    3. the risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
    4. procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that research project.
    5. the information is presented in a language which is understandable to the subject population.
    6. adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.
    7. where the IRB finds there may be a need for follow-up examination or care of subjects after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing subjects of this fact.

Note: An IRB finding that follow-up examination or care of the prisoner-subjects may be needed after the end of their study participation will necessitate a change in the standard Compensation for Injury section of the informed consent document. The change will need to

address the provision of long-term care for this subject population and must be prior approved by legal counsel to the IRB.

B. If a study utilizing prisoners as research subjects is federally funded, the IRB must send a letter to the Office for Human Research Protections (OHRP) indicating it has approved a study that will include prisoners, the category the study fits into as well as how the study satisfies the six (6) criteria noted under the regulations. A research study is not permitted to commence for Department of Health and Human Services (DHHS)-supported research until written approval is received from OHRP on behalf of the DHHS Secretary under the provisions of 45 CFR 46.306(a)(2).

Research Conducted in Pennsylvania State Department of Corrections
In Pennsylvania, the Department of Corrections has issued Policy Statement 2.1.2 which effectively bans the use of state prisoners in any medical experiments, cosmetic experiments, or pharmaceutical testing, with the exception for some testing involving treatment for AIDS and HIV infection. If a study utilizes prisoners from a state prison in Pennsylvania, approval from the Research Review Committee of the Commonwealth of Pennsylvania, Department of Corrections is required.

Research Conducted in the Federal Bureau of Prisons
The Federal Bureau of Prisons has adopted extensive regulations for investigators seeking to use federal prisoners as research subjects. Among other things, these regulations prohibit use of prisoners within federal facilities for “medical experimentation, cosmetic research, or pharmaceutical testing.” 28 C.F.R. 512.11(a)(3). In addition, strict limitations are imposed on incentives to prisoner/subjects, and investigators may not promise confidentiality to subjects who reveal a future intent to engage in criminal behavior.

When Subjects Become Prisoners During a Research Protocol
This policy applies whenever any human subject in a research protocol becomes a prisoner at any time during the protocol, e.g., after the research has commenced. This is necessary because it is unlikely that review of the research and the consent document contemplated the constraints imposed by the possible future incarceration of the subject. If a subject becomes a prisoner after enrollment in research, the investigator is responsible for reporting in writing this situation to the IRB immediately.

At the earliest opportunity after receiving the investigator’s notice or otherwise becoming aware of the prisoner status of a subject the IRB will review the protocol again with a prisoner representative as a member of the IRB.

The IRB will take special consideration of the conditions of being a prisoner. Upon this review, the IRB can either (a) approve the involvement of the prisoner-subjects’ in the research in accordance with this policy and all applicable regulations; or (b) determine that this subject must be withdrawn from the research.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XXVII**

Subject: **RESEARCH INVOLVING CHILDREN AS SUBJECTS**
(See, 45 CFR 46 Subpart D)

POLICY

The Children's Health Act of 2000 requires that all research involving children that is supported or regulated by the Department of Health and Human Services be in compliance with Subpart D of 45 CFR Part 46. The additional safeguards of Subpart D require the IRB to determine the level of risk and the prospect of direct benefit presented to the child by the proposed research. The Main Line Hospitals IRB adheres to the regulatory requirements for research with children as outlined in 45CFR 46 Subpart D and 21 CFR 50 Subpart D. These additional safeguards to protect the rights and welfare of subjects when some or all of the subjects are children apply regardless of the source of funding.

DEFINITIONS

Children - Federal regulations define "children" as persons who have not attained the legal age for consent to treatment or procedures involved in clinical investigations/research under applicable law of the jurisdiction in which the clinical investigation/research will be conducted. Under Pennsylvania law, persons under the age of eighteen (18) generally meet this definition of "children" with the exceptions noted below. As a result, permission of the child's parent(s) or guardian(s) must generally be obtained prior to the participation of that child in research.

Guardian - Under federal law, guardian means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. A child's "guardian" may provide legally effective informed consent for participation in research. If a guardian provides consent, the court order or legal authorization to consent to general medical care should be copied and included in the research records with the consent document. It is important to note that physical custody and legal guardianship may not be the same for some children, and that courts may only grant partial or joint custody in some cases. Review of the court order or other legal documentation establishing the guardianship is necessary to determine who may provide consent for participation in research on behalf of the child. Under the laws of the Commonwealth of Pennsylvania, foster parents or Children and Youth Services cannot consent to general medical care on behalf of a child, unless a court order or the consent of the parent has been obtained. Therefore, such persons do not meet the federal definition of "guardian" and cannot provide consent for the participation of a foster child in a research study. Only the birth or adoptive parent(s) can provide the legally authorized consent to participation in research.

Wards of the State - Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 and 45 CFR 46.407 or 21 CFR 50.53 and 21 CFR 50.54 only if such research is:

- related to their status as wards; or
- conducted in schools, camps, hospitals, institutions or similar settings in which the majority of children involved as subjects are not wards (45 CFR 46.409 or 21 CFR 50.56).

Where the proposed research involves Wards of the Commonwealth of Pennsylvania or any other agency, institution, or entity; an advocate will be appointed for each child who is a Ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis (i.e., see 45 CFR 46.409 (b) and, if applicable, 21 CFR 50.56).

- One individual may serve as an advocate for more than one child-Ward.
- The advocate will be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way, except in the role of advocate or member of the IRB, with the research, the investigator(s), or the guardian organization.

BACKGROUND

The provisions that permit a minor to be considered emancipated vary depending upon the circumstance. In the Commonwealth of Pennsylvania, a minor can be considered emancipated for one purpose, for example, obtaining birth control, but not for others. Unless a minor has been emancipated by court order, which should be confirmed by requesting a copy of the order, a minor should NOT be considered emancipated for purposes of consenting to participation in research.

Children who are wards of the Commonwealth of Pennsylvania or any other agency, institution, or entity can be included in research only under certain conditions.

For human subject research conducted in jurisdictions outside Pennsylvania, the MLH Legal Department determines who meets the definition of children as defined by FDA and DHHS and resolves conflicts among applicable laws. The investigator or the IRB will contact MLH Senior Counsel to assist in determining the legal definitions with respect to child or guardian under local law.

IRB CONSIDERATIONS

1. Child-subject assent means the child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, that the children are not capable of providing assent based on the age, maturity, or psychological state, or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children, and is available only in the context of the research, the IRB may determine assent of the children is not a necessary condition for proceeding with the research.

2. Parental permission means the agreement of the parents(s) (natural or adopted) or guardian (a person authorized under the law of Pennsylvania to consent on behalf of a child) to the participation of their child or ward in research. The IRB shall require that adequate provisions are made for soliciting the permission of each child's parents

or guardian. (45 CFR 46.408)

Where parental permission is required, the IRB may find that the permission of one parent is sufficient for research which does not involve greater than minimal risk, 45 CFR 46.404 - see Section D.1.a., or involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject, 45 CFR 46.405 - Section D.1.b.

Where research involves greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition, 45 CFR 46.406 - see Section D.1.c., or research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, 45 CFR 46.407 - see Section D.1.d., and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

3. Assent Waiver - the requirement to obtain child assent may be waived according to appropriate conditions:
    - outlined in the MLH IRB Policy XII: Informed Consent Documentation; ***OR***.
    - the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement (e.g., neglected or abused children) it may waive:
    - a. the consent requirements as outlined in the MLH IRB Policy XII: Informed Consent Documentation or
      b. the requirement for soliciting permission of each child's parents provided an appropriate mechanism for protecting the children who will participate as subjects is substituted and the waiver is not inconsistent with applicable law.

Assent Specifications

1. The assent of the child and permission of the parent(s) are required when in the judgment of the IRB the child is capable of providing assent and the study does not qualify for a waiver.

2. The IRB must determine for each protocol\ depending on such factors as the nature of the research and the age, status and condition of the proposed subjects whether none, all or some of the children are capable of assenting to participation.

3. In determining capability to assent, the IRB must take into consideration the age, maturity and psychological state of the children involved.

4. When the IRB determines assent will be required the IRB must also determine if assent is required to be documented.

5. When assent is required to be documented, to assure that the child has been given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity and condition. It will be obtained and documented as follows:
    a. Children aged 6 - 13 years, by investigator verification of explanation***.**
    b. Children aged 14 - 17 years, will read and sign the standard informed consent document prior to participating as a subject in the research and the investigator will sign the verification of explanation*****

c. Exceptions to a. and b. above are allowed only when the IRB has determined that, the capability of the children to be enrolled in the study is so limited that they cannot reasonably be consulted, or the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

*__Documentation of Investigator Verification of Explanation__
When assent is required by the IRB in some or all of the children verification of the explanation given to the child in obtaining the assent must be documented on the informed consent. The Verification of Explanation should be on the same page as the parent(s) or guardian(s) signature and be signed and dated by the investigator. It should read as follows:

Verification of Explanation

I certify that I have thoroughly explained the nature and purpose of this research including any discomforts and inconveniences which may occur to_____. He/she has had an opportunity to discuss it with me, to ask any questions and raise concerns. I have answered his/her questions and concerns and he/she has assented (affirmatively agreed) to participate in this research.

_____ _____
Principal/Sub-investigator signature Date

PROCEDURES
IRB Review
A. Determine permissibility of the research
The purpose of research activities involving children is appropriate to their age and represents one of the following four permissible categories of research:

1. *Research not involving greater than minimal risk* – This category applies only if the IRB finds that adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

2. *Research involving greater than minimal risk but presenting the prospect of direct benefit to an individual subject* – This category applies only if the IRB finds that:
    a. the risk is justified by the anticipated benefit to the subjects;
    b. the relation of the anticipated benefit to risk is at least as favorable to the subjects as that presented by available alternative approaches; and
    c. adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

3. *Research involving greater than minimal risk with no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition* – This category applies only if the IRB finds that:

    a. the risk represents a minor increase over minimal risk,
    b. the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations,
    c. the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or

amelioration of the subject's disorder or condition, and
d. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

4. *Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children* – This category applies only if the IRB finds that:

a. the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and
b. the Secretary, Department of Health and Human Services (DHHS), after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment, has determined that the research meets the criteria and ethical principles as found in 45 CFR 46.407, and
c. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

B. Assess risk/benefit ratio of proposed research to the children weighing the circumstances of the subjects under the study, the magnitude of risks that may accrue from the research procedures, and the potential benefits the research may provide to the subjects or class of subjects.

C. Determine that adequate provisions are made for soliciting the assent of the children when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB will take into account the ages, maturity and psychological state of the children involved. The requirement for assent may be made for all children, some children, none of the children, when assent is not required for some or all of the children the IRB documents the rationale.

D. Require in the case of a ward that the conditions and appointment of an advocate for each ward is made according to 45 CFR 46.409.

E. Examine informed consent document and assent document, if applicable and process.

Investigator Responsibilities

1. Provide for inclusion/exclusion of children in the proposed research according to 45 CFR 46 Subpart D.
2. Describe the process for obtaining assent and parental permission in the proposed research.
3. Solicit assent from the children as required by the IRB and permission of their parents or guardians.
4. Ensure appropriate documentation when a change in the guardianship status requires obtaining permission from the newly appointed guardian in order for the child to continue participation in the research.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **XXVIII**

Subject: **RESEARCH ACTIVITIES INVOLVING EXPOSURE OF RESEARCH SUBJECTS TO IONIZING RADIATION**

PURPOSE

Research studies involving ionizing radiation, radioactive materials and radiation producing devices, exposure to research subjects when the exposure is not considered standard of care must be reviewed by the Radiation Safety Committee.

DEFINITIONS

1. Ionizing Radiation: Radiation having sufficient energy that they dislodge electrons from atoms as they are absorbed by tissues. Ionizing radiations include high energy electromagnetic radiations, e.g., x-rays and gamma rays) and rapidly moving particles, e.g., alpha particles, cosmic rays, and high-energy protons, electrons, and neutrons. Ionizing radiations can be produced by machines that accelerate particles to high energies to produce radiation for use in therapeutic or diagnostic procedures, e.g., linear accelerators, x-ray machines, CT scanners. They can also be produced through the decay of radioactive isotopes such as those used in nuclear medicine procedures (e.g., ^{131}I or ^{99m}Tc), or PET studies (e.g., ^{18}F).
2. Magnetic Resonance Imaging (MRI): Research that involves magnetic resonance imaging (MRI), microwaves, ultrasound, visible light, ultraviolet light, and lasers do not involve ionizing radiations and do not require review by the Radiation Safety Committee.
3. Non-Ionizing Radiation: Microwaves, ultrasound, visible light, ultraviolet light, and lasers do not involve radiation with sufficient energy to dislodge electrons from atoms. Protocols involving non-ionizing radiation do not require review by the Radiation Safety Committee.
4. Nuclear Medicine: Protocols involving the injection of radiopharmaceuticals, such as those used in nuclear medicine procedures or PET scans.

Examples of studies that require review and approval by the Radiation Safety Committee

1. Any research protocols involving the use of investigational, non-Food and Drug Administration (FDA) approved, radiopharmaceuticals. A radiopharmaceutical is defined for this purpose as any drug, antibody, metabolic tracer, or other material labeled with a radioactive isotope.
2. Protocols using investigational non-FDA approved equipment or devices that produce ionizing radiation for either diagnostic or therapeutic purposes. These would include x-ray generating equipment as well as radiation-emitting devices such

as radioactive stents.

3. Studies with FDA approved radiopharmaceuticals that are needed for research purposes but would not normally be a part of the subjects' care and would therefore expose the subjects to a higher radiation dose than they would receive during routine care, e.g., extra ^{131}I studies for thyroid function or extra ^{99m}Tc such as MUGA scans for heart function.
4. Extra diagnostic imaging studies, for example, x-rays, CT scans, PET studies, SPECT studies, DEXA studies, using x-rays or radioactive isotopes that are needed for research purposes but would not normally be a part of the subjects' care and would therefore expose the subject to a higher radiation dose than they would receive during routine care.
5. Any protocol using an FDA-approved radiopharmaceutical or FDA-approved radiation-producing equipment or device for an off-label application.

PROCEDURES

Investigator Responsibilities

It is the responsibility of the investigator to inform the IRB of ionizing radiation, radioactive materials and radiation producing devices, exposure to research subjects when the exposure is not considered standard-of-care. The following information must be included on the Main Line Hospitals IRB (MLH) IRB Initial Submission within iMedRIS:

- A listing of the procedures involving ionizing radiation, radioactive materials and radiation producing devices, exposure to research subjects when the exposure is not considered standard-of-care radiation in the study
- The calculated level of exposure/dose.

Protocol Submission and Approval by the Radiation Safety Committee

Research involving ionizing radiation, radioactive materials and radiation producing devices, exposure to research subjects when the exposure is not considered standard of care use must be reviewed by the Radiation Safety Committee.

Investigators must submit the same version of the research protocol, informed consent and MLH IRB Initial Submission to the Radiation Safety Committee that will be reviewed by the MLH IRB.

Protocols to be reviewed by the Radiation Safety Committee should be sent to the Main Line Health Radiation Safety Officer for review.

Investigators must retain within their protocol records a copy of the Radiation Safety Committee approval and submit a copy of the approval to the MLH IRB for its records.

Protocol amendments which increase the radiation dose or require a change in body exposure site must be reviewed and approved by the Radiation Safety Committee.

Radiation Safety Committee

The Radiation Safety Committee has the authority to require modifications to the protocol and/or consent. All changes require final approval by the IRB. Research subjects may not be enrolled in the research until the approval of both the IRB and Radiation Safety Committee has been obtained.

IRB Review

To comply with the FDA and the Department of Health and Human Services (DHHS) guidelines and regulations, the IRB must assure subjects enrolled in an investigational study

are adequately informed about risk since the use of ionizing radiation in humans is associated with health risks in proportion to the amount of radiation received.

Note: The review by the IRB and Radiation Safety Committee can be done concurrently.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXIX

Subject: SUBJECT RECRUITMENT AND ADVERTISING

POLICY

All direct advertising and recruitment methods and content of the materials including the information contained in all advertisements and the mode of their communication when it may be seen or heard by potential subjects to solicit their participation in a research study. Advertisements cannot be displayed or put to use until the IRB has approved the final copy.

BACKGROUND

Direct advertising for study subjects is the start of the informed consent and subject selection process and IRB review is required for direct recruitment materials that are intended to be seen or heard by potential subjects to solicit their participation in a research study. The review is done to ensure that the information is not misleading to potential or current subjects. The IRB is required to assure equitable subject selection and is particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

Research projects often involve recruiting potential subjects using a variety of methods. Some of the more commonly used recruitment methods include flyers, posters, brochures, media advertisements, recruitment letters and word-of-mouth recruiting.

Federal regulations require that the IRB and investigators protect potential and current research subjects from coercion or undue influence, and also require investigators to use fair and equitable recruitment practices.

RECRUITMENT

The IRB has established the following guidelines for recruiting subjects to participate in research at MLH.

- Advertising and recruiting procedures must protect potential subjects' confidentiality.
- When obtaining the names of potential subjects from third parties, the investigator must consider whether any breach of confidentiality or privacy laws has occurred. For example, physicians must contact their patients for permission before releasing their names to a third party.
- Investigators are responsible for ensuring that approved procedures are followed by any third parties, e.g., specialists or social-service providers, who may be aiding in the recruitment and/or advertising process.
- The IRB does not generally support the use of widespread mass mailings or

unsolicited telephone calls to the MLH community.
- All proposed methods of recruitment must be described in the research protocol or IRB Application via iMedRIS and approved by the IRB.
- Investigators may not share names of previous research subjects with other investigators without permission from the subjects.

CONTENT OF ADVERTISING[24]

The IRB has established the following guidelines for advertisements, including recruitment scripts, seeking subjects to participate in research at MLH when intended to be seen or heard by potential subjects to solicit their participation in a research study:

1. Information should be limited to what is necessary for the potential subjects to determine their eligibility and interest.
2. All advertisements must be written in simple language, 8th grade reading level.
3. The following items may be included:
   - The name and address of the investigator or research facility
   - The purpose of the research or the condition under study
   - In summary form, the criteria that will be used to determine eligibility.
   - A brief list of benefits to subjects, if any
   - The time or other commitment required, number of visits, duration of study, etc.
   - The location of the research and person or office to contact for further information.
4. Advertisements may state that subjects will be paid but should not use bold or enlarged print or other means to emphasize payment or the amount to be paid.
5. Do not refer to payment in the header of the ad.

The following may NOT be included in the advertisement:

- Claims of safety, effectiveness, equivalence or superiority in reference to the drug, device or procedure under investigation.
- Use terms such as “new treatment”, “new medication”, or “new drug” without explaining that the test article is investigational.
- Use of bold or enlarged print or other means to emphasize payment or the amount to be paid.
- Use of exculpatory language.
- A statement or an implication of IRB or other institutional endorsement of the study.
- Claims that the subject will receive therapeutic benefit from participation in the study.
- Promise "free medical treatment" when the intent is only to say subjects will not be charged for taking part in the investigation.
- Make claims, either explicitly or implicitly about the drug, biologic, or device under investigation that are inconsistent with the Food and Drug Administration (FDA) labeling.

PROCEDURES

Investigator Responsibilities

The investigator must submit all draft and final copies of advertising materials to the IRB for review and approval at the time of initial submission or through an amendment at any time during the conduct of the study. In addition, the investigator must provide a description of

[24] Not included are brief listings of clinical trials on the internet when provided information is limited to basic trial design; communications intended to be seen or heard by health professionals, news stories, and publicity intended for other audiences such as a financial page advertisements directed toward prospective investors.

how the advertisement will be utilized to recruit subjects.

Distribution of Ads Within Main Line Health, Main Line Hospitals or other MLH Affiliate
Advertisements for direct recruitment intended to be seen or heard by potential subjects to solicit their participation in a research study cannot be displayed or put to use until the IRB has approved the final copy. Advertisements must also meet the requirements outlined in the MLH Administrative Policy on Advertising.

IRB Review
The IRB will review the procedures for recruitment and information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting subjects is not coercive. The IRB will review advertising to ensure that advertisements do not:

1. State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
2. Include exculpatory language.
3. Emphasize the payment or the amount to be paid, by such means as larger or bold type.
4. Promise “free medical treatment,” when the intent is only to say subjects will not be charged for taking part in the investigation.
5. Use of the term “new” in reference to a drug or device without explaining that the test article is investigational.

The IRB must review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB may review the final audio/video tape. When changes are required the IRB will review and approve the final copy of printed advertisements and final audio/video recording or transcripts.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXX

Subject: PAYMENT TO RESEARCH SUBJECTS AND RESEARCH PERSONNEL

POLICY

The Main Line Hospitals Institutional Review Board (MLH IRB) must review and approve any proposed payments to research subjects to determine that the amount of payment and the proposed method and timing of disbursement are neither coercive nor present a potential for undue influence on the subjects. Institutional Review Board

BACKGROUND

The IRB recognizes that there are monetary costs involved with participation in clinical research, for example, parking, gasoline expense, childcare services, and loss of time at work. Research subjects should not be disadvantaged by their participation in research, and therefore appropriate compensation for time/expenses may be approved by the MLH IRB. However, undue influence/inducement is to be avoided. Undue influence may be seen as inducement so high that were it not for the amount, the subject would not enter or continue to participate in the study.

Payment to research subjects in studies is not considered a benefit; rather, it should be considered compensation for time and inconvenience associated with participation in research activities.

COMPENSATION AND PAYMENTS TO RESEARCH SUBJECTS

The IRB has established the following guidelines for compensation and payment to research subjects at MLH.

- Payments may be in the form of cash or non-cash.
- Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. In most cases involving continued participation, compensation should be given on a reasonable prorated basis. Compensation may not be withheld contingent on the subject's completion of the study.
- The compensation for participation in a trial offered by a commercial sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
- The use of a completion bonus is ordinarily discouraged. When a completion bonus is proposed, the IRB will determine whether the amount paid as a bonus for completion is reasonable and not large enough to unduly influence subjects to remain as a study subject when they would otherwise have withdrawn.
- Advertisements may state that subjects will be compensated or paid, but should not emphasize the payment or the amount, by such means as larger or bolded type, or

prominent placement in the ad itself.

- As a rule, the IRB will not approve cash payments to children. Children receive, if anything, non-cash gift certificates of a small amount, or something else non-cash, such as movie theatre passes or tickets to a children's musical event. The parent may receive cash, to help defray expenses such as parking, gasoline or meals associated with their child's participation in the research study.

PROCEDURES

Investigator's Responsibilities

The amount and schedule of all payments should be presented to the IRB at the time of initial review. The investigator will provide a detailed description of proposed compensation as requested within the IRB iMedRIS application. All information concerning payment, including the amount and schedule of payment(s), must be described in the informed consent document. Procedures for prorating payment should the subject withdraw should be included in the IRB application and informed consent document(s). Subjects should be paid in proportion to their time and inconvenience as a result of their participation in the research study.

Any changes in subject compensation or flexibility of the payment schedule must be reported to the IRB as a modification prior to implementation.

IRB Review

The IRB will review proposed payments to determine that:

- The amount of payment and the proposed method and timing of disbursement are neither coercive nor present an undue influence to enroll or stay in the study when the subject would otherwise have withdrawn.
- Credit for payment accrues as the study progresses and is not contingent upon the subject completing the entire study.
- Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
- All information concerning payment, including the amount and schedule of payments is set forth in the consent document.

PAYMENTS TO RESEARCH PERSONNEL

Payments to non-study personnel in exchange for referrals of potential subjects, finder's fees, are not allowed.

Payments or gifts to study personnel designed to accelerate recruitment that will be tied to the rate or timing of enrollment, bonus payments, are not permitted.

Cash or cash-equivalent payment to health care providers and research personnel for referral of subjects or potential subjects is not permitted.

Payments, including offers for unrestricted grants/gifts, from sponsors to research staff or organization that are tied to the rate or timing of research subject recruitment, "bonus recruitment payments", are not allowed.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. XXXI

Subject: IRB RECORD KEEPING

PURPOSE

The purpose of this policy is to describe recordkeeping activities and record retention for Main Line Hospitals Institutional Review Board (MLH IRB) activities that comply with federal regulations and MLH policy. The IRB will prepare and maintain adequate documentation of IRB activities per 45 CFR 46.115 and 21 CFR 56.115, including the following:

POLICY

The Office of Research Protections (ORP) maintains records relating to research, including materials submitted by investigators for IRB review, or exemption, documentation of IRB activities, and other required records, such as IRB correspondence, rosters, and policies. All records are retained in a secure manner that allows for a review of the history of IRB actions and for inspection by authorized personnel. Records are maintained for a minimum of 7 years after completion[25] of the research. Refer to the MLH Administrative Policy on Records Management (Retention and Destruction) for additional information.

PROCEDURES

IRB Records

The MLH IRB through ORP will prepare and maintain adequate documentation of IRB activities including the following for research submitted for expedited or full board review:

1. All available documents related to a research study including, but not limited to:
    a. IRB Application submissions via iMedRIS, Conflict of Interest Disclosure forms
    b. Protocol
    c. Grant (if applicable)
    d. Investigator's Brochure (if applicable)
    e. Consent/Assent Form(s)
    f. Recruitment and advertisement materials
    g. Reports of unanticipated problems and statements of significant new findings provided to subjects
    h. Reports of injuries to subjects
    i. Data safety monitoring reports
    j. Amendments
    k. Noncompliance
2. IRB Minutes including documentation of IRB determinations required by the regulations and protocol specific findings supporting determinations
3. Records of Continuing Review activities including all supporting documentation
4. Copies of official correspondence between the IRB and investigators
5. IRB Membership rosters

[25] For studies which are closed prior to study completion the termination/closure date, withdraw date is used.

6. IRB determinations for exempt research including citations of the specific categories justifying the exemption. and supporting documentation including copies of documents submitted and associated correspondence.
7. Quality improvement and non-human subjects research determinations along with supporting documentation including copies of documents submitted and associated correspondence.
8. For items reviewed by expedited procedure, the justification for using the expedited procedure, the actions taken by the reviewer including documentation of IRB determinations required by the regulations and protocol-specific findings supporting determinations and the MLH IRB Expedited Reviewer notations via iMedRIS.

IRB Records Storage and Availability
ORP will ensure that all records are stored confidentially in a secure location.

IRB records are accessible for inspection and copying by representatives of the sponsor of the research, authorized representatives of federal agencies, and by other authorized agents of regulatory or accrediting organizations. Complete study records are accessible to all IRB members.

Investigator Records
Investigator records are considered the official research file. The IRB office only maintains copies of documents sent to the investigator. It is the investigator's responsibility to maintain adequate documentation of research procedures/process. In case of a request to review the file all information must be readily available to be reviewed by the appropriate individuals in a reasonable manner. Investigator records must comply.

Records are maintained in accordance with the MLH Administrative Policy on Records Management (Retention and Destruction). Additional requirements for records retention may apply depending on the type and/or sponsor of the research.

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Revision Date: 12/01/23

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD
POLICY AND PROCEDURE MANUAL

Policy No. **XXXII**

Subject: **QUALITY ASSURANCE AND COMPLIANCE REVIEWS OF APPROVED RESEARCH, IRB RECORDS, INVESTIGATORS AND RESEARCH STAFF**

PURPOSE

The purpose of a quality assurance and quality improvement (QA/QI) program is to increase awareness of regulatory requirements, to ensure documentation supports regulatory and Main Line Hospitals Institutional Review Board (MLH IRB) requirements and to ensure the protection of human subjects.

PROCEDURES

The MLH IRB may review at any time all research records, including but not limited to informed consent documents, regulatory files, IRB files, research subjects' records and research subjects' medical records, record storage and results of procedures and tests performed during the course of the research. A minimum of four (4) QAQI reviews will be completed annually.

Office of Research Protections (ORP) staff has the authority to observe the informed consent process and to interview subjects either during or after their participation in research activities. ORP working jointly with the MLH Compliance Department will conduct the records review. Another party not affiliated with MLH institution may perform the records review.

COMPLIANCE REVIEWS

1. Random/Routine: ORP working jointly with the MLH Compliance Department will randomly select approved research studies. The criteria for selecting research studies may include, but not limited to:
   - those involving high risk to subjects.
   - those involving vulnerable populations.
   - those with high enrollment.
   - investigator initiated.
   - Investigators selected at the discretion of the IRB or IRB Chair
2. For cause: This review is performed when concerns regarding compliance, protocol adherence, or subject safety are brought to the attention of the IRB.
3. Request by Research Team: An investigator or research coordinator may request an on-site review to assist in keeping records and procedures in compliance with federal regulations and institutional policies or to prepare for an external audit by a sponsor or federal agency.
4. IRB Records review: ORP working jointly with the MLH Compliance Department will review the IRB files, including IRB minutes, justification for use of any expedited

procedures and IRB determinations of those studies selected for a compliance review.

Notice of Review
Prior to initiation of a compliance review, the investigator will be notified by ORP or the MLH Compliance Department. Generally, when conducting routine compliance reviews at least one-week advance notice is provided. When conducting for-cause audits, the visit may be unannounced or scheduled with minimal advanced notice.

Elements of Documentation Review
1. Before the review, ORP will review the IRB study file and all documentation related to the study including:
    a. Sponsor protocol
    b. Consent form(s) including verification that required consent elements are included.
    c. Continuation review/progress reports
    d. Amendments/modifications
    e. Unanticipated problems
    f. Protocol deviation(s)
    g. Complete study record from IRB database, to assure all fields are completed Accurately.
    h. IRB minutes to assess appropriateness of discussions and determinations documented and quorum requirements were met and maintained.
    i. The appropriate IRB determinations are documented when expedited procedures are used
    j. Any monitoring or auditing activities deemed appropriate by the IRB have been Implemented.
    k. Appropriate conflict of Interest forms are on file.

Applicable information is entered into the Quality Assurance and Compliance Reviews of Approved Human Research Studies Form for the study. This form or an alternate form may be used to capture required information specific to a study.

2. During the review, the investigator or designee will:
    a. Provide the regulatory binders and subject study files.
    b. Make available the use of a quiet space to review the study files.
    c. Be available during the compliance reviews to address questions.

3. During the review, ORP and/or the MLH Compliance Department will conduct a comprehensive review of IRB records and investigator study records, paper and/or electronic, to determine at a minimum:
    a. Executed subject informed consent and HIPAA authorization forms are appropriately documented and maintained.
    b. Study records are stored as described in the IRB application, protocol and consent form(s)
    c. Monitoring has occurred according to the protocol and/or IRB application.
    d. Appropriately trained personnel have conducted the consent process.
    e. All study personnel have been approved by the IRB and a delegation log is available, when applicable.
    f. IRB Correspondence is appropriately maintained.
    g. Test article accountability is appropriately maintained, when applicable.
    h. Screening logs are appropriately maintained, when applicable.
    i. Detailed review of protocol files, regulatory binders.

4. Additional activities performed during compliance reviews may include:

a. contacting research participants.
b. observing research sites when informed consent process is being conducted.
c. reviewing advertisements and other recruiting materials.
d. reviewing projects to verify from sources other than the researcher that no unapproved changes have occurred since the previous review.
e. conducting other monitoring activities as deemed appropriate by the IRB.

Information is recorded on the Quality Assurance and Compliance Form for the study. Additional documents may be used to capture subject specific information or the IRB Records review. After the review and when appropriate, preliminary findings and corrective actions, when necessary, are discussed with the investigator or designee.

Significant findings identified during the review are relayed within two business days to the IRB Chair, ORP Director and the MLH Chief Compliance Officer. If preliminary findings so indicate, the IRB may take appropriate action to ensure the safety and welfare of the subjects.

Reports of Findings
After the compliance review, a report of findings is prepared by ORP and/or the MLH Compliance Department. The report will provide a summary of the findings, including the identification of areas which need improvement and recommendations for improvement, when applicable.

a. Reports with minor findings and corrective actions are generally provided to the investigator, IRB Chair and ORP Director and the MLH Chief Compliance Officer within one month of the compliance review.

b. Reports containing significant findings are provided to the investigator, IRB Chair and ORP Director and the MLH Chief Compliance Officer approximately 5 business days dependent on availability of all relevant information. Potential noncompliance follows the MLH IRB Policy on Noncompliance (XX). Corrective action plans as a result of noncompliance or other findings are reviewed against current MLH IRB Policies and Procedures to determine any gaps. Identified gaps are reported to the Institutional Official (IO).

c. All findings are reviewed against current MLH IRB Policies and Procedures to determine any gaps which are used to revise policies and procedures.

Copies of audit reports and correspondence are maintained electronically.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **XXXIII**

Subject: **Jurisdiction Over Clinical Research**

POLICY

The Main Line Hospitals Institutional Review Board (MLH IRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities subject to review and approval by the MLH IRB. The purpose of this policy is to define activities which engage** the institution in research and require review and approval by the MLH IRB. This policy also addresses the conditions under which non-affiliated individuals[26] and/or institutions may conduct research at the Main Line Health System.

PROCEDURES

The Office of Research Protections (ORP) is responsible for, among other activities related to human research, providing direction and assistance to the research community at Main Line Health regarding MLH IRB jurisdiction over research engaged in, by, or with the participation of, any MLH Affiliate. When questions arise regarding the jurisdiction of the MLH IRB and research, the MLH Institutional Official, through the MLH IRB and ORP shall make the final determination.

Main Line Health System Engagement

The research conducted throughout the Main Line Health System (MLHS) is divided into three categories. Activities defined in Category A below mandate review by the MLH IRB. These scenarios are not intended to be exclusive and there may be situations where specific facts and circumstances must be examined to determine the jurisdiction of the MLH IRB[27].

Category A – Review required by MLH IRB

1. **Protocols that require hospital involvement**. This category includes research studies in which any part of the research is carried out within Main Line Hospitals with services provided by Main Line Hospitals or with the involvement of a Main Line Health affiliated entity, MLH Affiliate. A MLH Affiliate is defined to be an entity of which Main Line Health, Inc., or a Main Line Health subsidiary, is the parent organization[28]
2. **Research in which funding is received or administered by or contracted with Lankenau Institute for Medical Research (LIMR) or other MLH Affiliate.** This

[26] Refer to footnote 31 for additional information.
[27] In limited circumstances, the MLH IRB may consider entering into an IRB authorization agreement for review by an external IRB.
[28] Main Line Hospitals, Inc., if not referenced separately in this policy, is included among MLH Affiliates.

category includes research which is sponsored, grant funded, MLH Affiliate supported or otherwise funded by a MLH Affiliate.

3. **Employees of Main Line Health, Main Line Hospitals or other MLH Affiliate**. This category includes research studies conducted by employees of Main Line Health, Main Line Hospitals, or other MLH Affiliate.
4. **Research conducted to meet a Main Line Hospitals (or other MLH Affiliate) Educational Requirement or Institutional Responsibility.** This category includes research required to complete an approved Main Line Hospital's Residency, Fellowship Program or other MLH Affiliate approved educational requirement.
5. **Research involving the use of non-public information belonging to Main Line Health, Main Line Hospitals, or Other MLH Affiliate**. This category includes activities involved in contacting or identifying research subjects or potential subjects including any activities which involve obtaining, from any MLH Affiliate, identifiable private information or identifiable specimens for research purposes. This category includes the use or disclosure of protected health information (PHI) for research purposes. May require review by the Chief Privacy Officer for MLH.

Category B –Review by MLH IRB at Investigator's Option[29]

Independent Physicians with Medical staff appointment at Main Line Hospitals or other MLH Affiliate. This category includes research studies that are conducted exclusively in a physician's office[30], the physician is not an employee of Main Line Health, Main Line Hospitals, or other MLH Affiliate; and the research does not fall within any of the activities described in Category A. In this category, the only relationship the physician has with Main Line Health or a MLH Affiliate, is medical staff membership. If Main Line Health or a MLH Affiliate is not engaged[31] in the research then review by the MLH IRB is optional. The MLH IRB or an external IRB may review the research.

Category C – Review by a Unaffiliated/External IRB

The MLH Institutional Official (IO), through the ORP Director, and as necessary the IRB Chair, maintains authority to determine which studies, that would otherwise be reviewable by MLH IRB under Category A, may be classified as Category C studies and reviewed by an unaffiliated/external IRB. The unaffiliated/external IRB must be accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRP) and must agree to the division of responsibilities as required by MLH IRB. A written agreement, contract or authorization agreement is required between the MLH IRB and the unaffiliated/external IRB and will include a division of roles and responsibilities between the parties.

During the ORP review of the investigator's request to use an unaffiliated/external IRB a screening process will be completed to confirm the protocol conforms with MLH IRB and MLHS standards for protection of human subjects, acceptable practice(s) to deliver care, and institution and investigator commitment to support the research activity. The new protocol submission screening process includes reviewing all documents submitted to ORP at the time of initial review, as is done with all applications to the MLH IRB. A fully executed/signed MLH

[29]When MLH IRB review is conducted under Category B, MLH involvement in the study is limited to IRB review.
[30]Research that is conducted by non-employees at non-MLH locations (not owned by Main Line Health, Main Line Hospitals or other MLH Affiliate) is not covered under the Main Line Hospitals Federalwide Assurance.
[31]Refer to OHRP Guidance on Engagement of Institutions in Human Subjects Research for a complete discussion on engagement of institutions and individuals in research.

conflict of interest disclosure form for each researcher, and Transmittal Form MUST be included with the application. Additionally, a formal screening of the qualifications of the unaffiliated/external IRB is conducted and documented. Screening of the unaffiliated/external IRB is completed using the ORP screening worksheet and checklist for use of external IRB. Once the screening is completed a written IRB Authorization Agreement (IAA)/contract will be executed and signed by the IO. The worksheet, checklist and final IAA/written agreement are to be retained by ORP.

In studies transferred to an unaffiliated/external IRB, the MLH IRB, acting as the MLH Privacy Board maintains the authority to grant HIPAA waivers of authorization. MLH IRB approves HIPAA authorization language when applicable.

Process

A. MLH IRB Fees

All research which is industry sponsored is subject to MLH IRB fees. Some external grant funded studies may be subject to MLH IRB fees. The fees may vary depending on the type of review conducted. A MLH IRB processing fee is charged for industry sponsored studies reviewed by an unaffiliated/external IRB.

All research reviewed by the MLH IRB in Category B. "*Review by MLH IRB at Investigator's Option"*, conducted by Independent Physicians is subject to MLH IRB fees. The fees may vary depending on the type of review conducted.

B. Institutional Department Review

When a research project is reviewed by the MLH IRB, the review by the Institutional Department(s) outlined in the table below is required. **Institutional Department review is required for each type of research that applies to the investigator's project.** *Research in Category B, "Review by MLH IRB at Investigator's Option", when reviewed by the MLH IRB does not require any MLH institutional department review other than those of supporting hospital departments or supporting MLH Affiliate providing services.*

*Type of Research	Department Chair(s)/ Clinical Division Chief(s)	Supporting Hospital Department(s) (e.g., pharmacy or lab)	Nursing Research Council Chair	LIMR Administration	Medical Education
Resident/ Fellow or other Educational Research	X	X		X	X
**Sponsored Research	X	X		X	
Nursing Research	X***	X	X	X	
Non-Funded Research	X	X		X	

*More than one type of research may apply to your project. Institutional Department review is required for each type of research involved in your project (i.e. a project may be a sponsored, nursing research project and would require the signatures listed for each type).
**Refer to Category A.2, above for more information.
*** Nursing Research requires the signature of the appropriate Nurse Manager and/or supervisor.

Other Research conducted by non-affiliated[32] individuals and/or institutions at Main Line Health System

Research is not permitted to be conducted at the Main Line Health System by non-affiliated individuals and/or institutions. The MLH IRB recognizes that collaborative research programs may originate at non-affiliated institutions. Collaborative research protocols may only be submitted to MLH IRB by affiliated individuals who are sufficiently active collaborators in the research to assume full responsibility for the ethical and scientific conduct of the research at the MLH System, entity or MLH Affiliate.

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[32]The following categories are considered to be affiliated with Main Line Health 1.) employees of Main Line Health, Main Line Hospitals or other MLH Affiliate; 2.) participant in a Main Line Hospital's Residency, Fellowship Program or other MLH Affiliate approved educational requirement; 3.) have Medical staff appointment at Main Line Hospitals or other MLH Affiliate; 4.) are part of the covered work-force at Main Line Health, Main Line Hospitals or other MLH Affiliate. When non-affiliated individuals are engaged in a collaborative research project on any campus or have access to Protected Health Information (PHI) of Main Line Health System, Main Line Hospitals or MLH affiliate, individuals must have appropriate permissions (e.g. vendor clear and/or other necessary or required credentialing).

MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD POLICY AND PROCEDURE MANUAL

Policy No. **XXXIV**

Subject: **Main Line Hospitals Institutional Review Board (MLH IRB) Policy and Procedures Maintenance**

PURPOSE

The purpose of this policy is to state the Main Line Hospitals Institutional Review Board (MLH IRB) commitment to maintain and follow up to date policies and procedures that adhere to regulations and ethical principles pertaining to research with human subjects.

POLICY STATEMENT

Following federal regulations and guidance supported by institutional policies assures that the rights and welfare of the human research subjects will be overseen and protected in a uniform manner.

Changes to applicable laws, regulations/guidelines, the Association for the Accreditation of Human Research Protection Programs (AAHRPP) standards, any recommendations made through regulatory agencies inspections as well as to the policies and procedures of the institution, may require the creation or revision of policies, procedures and/or forms.

PROCEDURES

1. The MLH IRB Policy and Procedure Manual is maintained by the Office of Research Protections and contains documents which combine both policy statements and procedures. All documents contained in the manual will include a number and contain an origination/revision date. Refer to requirements in the MLH Administrative Policy, Policy Manager Template for additional information.

    a. New or revised MLH IRB policies are prepared and reviewed by the Office of Research Protections (ORP), with input from the MLH IRB Chair, and with input from the Institutional Official (IO), MLH Legal and MLH Compliance as necessary. Following approval, investigators, researcher staff, management and staff will be informed of the new or revised policies. When IRB members are notified at an IRB meeting, this will be noted in the minutes for the meeting. Training is provided to investigators, research staff, management, staff members and IRB members as necessary.

    New or revised MLH IRB Policies are approved by the Quality and Safety Committee (QSC) of the Main Line Hospitals Board through the IO as required in MLH Administrative Policy: Human Research Protection Program.

b. New or revised MLH IRB procedures are reviewed and approved by the ORP Director, with input from the MLH IRB Chair as necessary. Training is provided to investigators, staff members and IRB members as necessary. When MLH IRB policies and procedures are combined in one document, changes to the procedure section may be made without changes to the Policy statement.

2. New or revised MLH IRB forms and checklists are reviewed and approved by the ORP Director and MLH IRB Chair as necessary. All forms and checklists will include a revision date.

3. The IRB Policy and Procedure Manual and any future modifications are made available to all IRB members and individuals conducting or reviewing human subject research. Policies, procedures and accompanying materials, e.g., forms, guidance, will be posted and made available on the ORP website. Communication will be made about new or revised policies and procedures through various MLH and IRB communication mechanisms.

REVIEW

No less than once every two years, all policies, procedures and forms are reviewed by the ORP Director to identify necessary revisions. The review date will be documented in the manual.

Any necessary revisions are processed according to steps outlined in Procedures.

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