

PROCEDURES

For Compliance with Federal Regulations

For the Protection of Human Research Subjects

for

INSTITUTIONAL REVIEW BOARDS

of

MAIN LINE HOSPITALS, INC.

Including:

Bryn Mawr Hospital
Lankenau Medical Center
Paoli Memorial Hospital
Riddle Hospital
Bryn Mawr Rehabilitation Hospital
Lankenau Institute for Medical Research

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PREFACE and BACKGROUND

Main Line Hospitals, Inc. is committed to safeguarding the rights and welfare of persons participating in research conducted under its jurisdiction.

To that end it is cognizant of the Declaration of Helsinki - a code of ethics for clinical research - which had been approved by the World Medical Association initially in 1964 and most recently in 1989. Additionally, Main Line Hospitals, Inc. (MLH) subscribes to and abides by the Belmont Report which contains a statement of basic ethical principles governing research involving human subjects which was issued by the National Commission for the Protection of Human Subjects in 1979. Aware of its role in perpetuating ethical standards in the application of sound medical research, MLH maintains the above referenced documents on site as a written embodiment of the ethical foundation for all research conducted on MLH campuses.

These documents also served as a foundation for the United States Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) when creating a mechanism to protect and regulate the conduct of human research in America. This was done by incorporating the ethical standards promulgated in the above national and international documents into the creation of what is now known as an Institutional Review Board (IRB). It is through the operation of the IRB that persons participating as subjects in research are assured treatment in accordance with basic ethical principles, namely, respect for persons, beneficence and justice. This IRB mechanism is codified at Title 45 Part 46 and Title 21 Parts 50 & 56 of the Code of Federal Regulations.

MLH serves as part of this mechanism to assure the safeguarding of the rights and welfare of research participants through its IRB which operates in accordance with the federal regulations promulgated by the FDA and the DHHS. It has entered into an Assurance with the Office for Human Research Protection (OHRP) a division of the DHHS, as a participant in federally conducted or supported research. As such, it has assured the OHRP that it will comply with the federal regulations, ethical principles and guidelines for the protection of human research subjects as set forth in the Belmont Report. This Assurance is an agreement between MLH and the OHRP setting forth the specifics as to how it will protect the welfare of research subjects.

The IRB Procedures contained herein provide the IRB and research investigators with the necessary information to comply with the MLH's policy and principles relating to investigations involving human participants. The Procedures contain the framework for the conduct of ethical human research while citing the legal obligations which control its parameters.

INSTITUTIONAL REVIEW BOARD PROCEDURES FOR COMPLIANCE WITH FEDERAL REGULATIONS GOVERNING THE PROTECTION OF HUMAN RESEARCH SUBJECTS

PURPOSE

According to federal regulation, all non-exempt research involving human subjects funded by the government or submitted to the Food and Drug Administration (“FDA”) must be approved by an Institutional Review Board (“IRB”). The purpose of the IRB is to provide institutional assurance that the rights and welfare of all human beings who participate as research subjects under its jurisdiction are protected.

INTRODUCTION

The Board of Trustees of Main Line Hospitals, Inc. has approved the establishment of an Institutional Review Board (“IRB”), composed of three subcommittees under a Federal-Wide Assurance (FWA) with the Office of the 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, and the Lankenau Institute for Medical Research. The three IRB subcommittees are at Bryn Mawr, and Paoli Hospitals and Lankenau Medical Center. Any of the 3 subcommittees may review research conducted at any site included under the FWA or within the Main Line Health System.

Main Line Hospitals, Inc. (“Hospitals”) is committed to safeguarding the rights and welfare of persons participating in research conducted under its jurisdiction.

For the purposes of this IRB Policy and Procedure Manual of the Main Line Hospitals, Inc. Institutional Review Board the following definitions are applicable:

1. Research

- a. *DHHS regulations - “a systematic investigation 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. 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 conducting research obtains (1) Data through intervention or interaction with the individual or (2) Identifiable private information.”
- 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

- a. DHHS Regulations - Meets the definition of research involving human subjects as defined in the DHHS regulations.
- b. FDA Regulations - Meets the FDA definition of clinical investigation involving human subjects as defined by FDA regulations.

It is through the operation of the IRB that persons participating as subjects in research are assured treatment in accordance with basic ethical principles, namely, respect for persons, beneficence and justice. The principle tenets of the IRB are in accordance with Title 45 Part 46 and Title 21 Parts 50 & 56 of the U.S. Code of Federal Regulations.

The IRB serves to assure the safeguarding of the rights and welfare of research participants promulgated by the Food and Drug Administration (FDA) and the DHHS. Through its FWA, Hospitals has assured the DHHS that it will comply with the federal regulations and the ethical principles and guidelines for the protection of human research subjects as set forth in the Belmont Report. This Assurance is an agreement between Hospitals and the OHRP that sets forth the specifics as to how Hospitals will protect the welfare of research subjects. A separate, complete MLH IRB Policy and Procedure Manual is maintained in the Office of Research Affairs (ORA). It contains detailed information regarding the operations of and the procedures governing the IRB and its protection of human subjects.

POLICY

All research will be well-conceived and well-conducted so human subjects are not exposed to any unnecessary risk as required by federal regulations. The IRB has the authority to approve, modify to require approval, disapprove, suspend, and terminate research to protect the rights, welfare and privacy of research subjects. The IRB has authority to observe, or have a third party observe, the consent process and the conduct of the research.

All research involving humans as subjects, except those categories specifically exempt by federal regulation, will be reviewed by the IRB which has been established under the FWA.

Human subjects in research may not be permitted to participate in research until the IRB has reviewed and approved the research protocol and informed consent document prepared in accordance with and to the extent required by 45 CFR 46.116 and 21 CFR 50.25. The IRB has the authority to waive the informed consent requirement in research involving emergency medical situations pursuant to 21 CFR 50.24 Exception from informed consent requirements for emergency research. In addition, research may not begin until required institutional approvals are obtained and federal grants which are awarded to the institution are reviewed by the IRB.

All protocols approved by the IRB will be reported to ORA. The ORA will report to the Institutional Official, who will report to the Quality and Patient Safety Committee (QPSC) of the [Main Line Hospitals] Board. The QPSC or other officials or committees may disapprove protocols approved by the IRB but may not approve protocols disapproved by the IRB.

The IRB shall continue to review the progress of an approved protocol as long as research subjects are in follow-up and or/study related activities are on-going.

This policy applies, regardless of the source of funding and location of the study, to all biomedical and behavioral research activities, as enumerated in Policy IV, Part 3, Jurisdiction over Research Involving Human Subjects”.

In addition to the Institution's FWA, a copy of the IRB Policy and Procedure Manual and any future modifications, is available to all IRB members and individuals at the Hospitals conducting or reviewing human subject research on the Office of Research Affairs website at www.limr.org/ora.

The policy and procedure manual is maintained by the ORA and changes or additions to policies are approved by the QPSC, MLH Legal, IRB Chairman and Director of Research Affairs.

Part 1
GENERAL PROCEDURES

BRYN MAWR HOSPITAL**LANKENAU HOSPITAL****PAOLI****HOSPITAL LANKENAU INSTITUTE FOR MEDICAL RESEARCH**

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**Part 1****Policy No. I****Subject: MAIN LINE HOSPITALS EDUCATION REQUIREMENTS FOR INDIVIDUALS INVOLVED
IN HUMAN SUBJECTS RESEARCH ACTIVITIES AT MAIN LINE HOSPITALS**

Policy

Main Line Hospitals is responsible for providing, through the Office of Research Affairs at Lankenau Institute of Medical Research (LIMR), 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 clinical research studies using human subjects at Bryn Mawr Hospital, Lankenau Medical Center, Paoli Hospital, Riddle Hospital and Bryn Mawr Rehabilitation Hospital. This policy also applies to all IRB administrative staff, and all IRB members. Each person covered by this policy must successfully complete the education program administered by LIMR. Certification of successful completion of the training must be renewed every three years.

Procedure

The Education Program in Human Subjects Research at MLH consists of the following:

1. An on-line computer based training program that must be completed by all current and new investigators, their research support staff, IRB Members and IRB administrative support staff. Successful completion of the computer based program will provide a certification of the training in Human Subjects Research.
2. Continuing education and training is required of clinical investigators, their research support staff, IRB Members and IRB administrative support staff.

Process**Computer Based Training and Continuing Education:**

The LIMR Office of Research Affairs uses a subscription on-line service to complete the training requirement for human subjects researchers, research support staff, IRB members, and IRB Administrative staff. The program is sponsored by the Collaborative IRB Training Initiative (CITI). Completion of the computer based curriculum is required for certification to conduct or be involved in human subjects research. Investigators and their research support staff, IRB administrative staff, and IRB members are required to renew their certification in human subjects research every three years by successfully completing the on-line CITI Program.

8/13/01

The 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 will be granted. This includes, but is not limited to, investigators, sub-investigators, staff, coordinators and nurses involved in the conduct of a study. Such individuals are required to renew their certification in human subjects research every three years from the time they successfully complete the Basic CITI training course.

The link to the on-line CITI Training course is available on the Office of Research Affairs website at <http://www.limr.org/ORA> or directly at www.citiprogram.org There are several groups to choose from as outlined below.

Group 1 - Biomedical Research: For research personnel who engage in Biomedical research

Group 2 - Social and Behavioral Research: For research personnel who engage in Social and Behavioral research which does not involve biomedical procedures. Research personnel who engage in biomedical research must also complete the Group 1 Module.

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.

Group 4 - IRB Members: for IRB members and staff. This group does **NOT** satisfy the educational requirements for Groups 1, 2 or 3.

Origination Date: 12/2003

Revision Date: 02/04/13

**PART 1, POLICY I
REVISED 10/01/12**

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN LINE
HOSPITALS INSTITUTIONAL REVIEW BOARD****Part 1****Policy No. II.****Subject: INTRODUCTION TO THE INSTITUTIONAL REVIEW BOARD**

The ORA has prepared these procedures to facilitate management of research activities on its part, and to provide clear direction to Research Investigators for compliance with IRB decisions, conditions and requirements as well as those government regulations that apply to research.

A. IRB Membership.

The Main Line Hospitals Board of Trustees appoints the Chair and members of the IRB and modifies the membership from time to time. The names of the appointees are submitted to the Board for approval by the President, Lankenau Institute for Medical Research. The President, Lankenau Institute for Medical Research is responsible for the oversight of research activities and IRB functions and has the legal authority to act and speak for the institution in all matters relating to research in consultation with the President and CEO Main Line Health and in cooperation with the MEC, JCC, investigators, and department heads.

There are two types of IRBs. One is for the review of general research and is called a General Committee. The Institution has one General Committee which is composed of three units with overlapping membership: one shall meet at Lankenau Hospital; one shall meet at Bryn Mawr Hospital; and one shall meet at Paoli Memorial Hospital (Lankenau, Bryn Mawr and Paoli Memorial Hospitals are sometimes referred to individually herein as a "Campus" or collectively as the "Campuses"). The other type of IRB is for the review of research involving behavioral science and is called a Behavioral Science Committee. For the purposes of these Procedures, either or both types of IRBs shall be referred to as "the IRB" or "the Committee."

There shall be a Vice Chair of the IRB from each campus who shall be appointed by the Main Line Hospitals Board of Trustees on recommendation by the President, Lankenau Institute for Medical Research. Each Campus Vice Chair shall assume the duties of the Chair, relative to such Campus, in the Chair's absence or at the Chair's discretion.

The General Committee consists of the number of members per Campus and their alternates, as set forth in the Institutional Review Board/Independent Ethics Committee Registration who are each appointed by the Main Line Hospitals Board of Trustees on recommendation by the President, Lankenau Institute for Medical Research. There shall be no limitation on the number of

consecutive terms that any IRB member may serve. IRB membership shall be in accordance with 45 CFR 46.107 and 21 CFR 56.107. The members represent diverse backgrounds, experience, and expertise, and together possess the professional competence necessary to review the specific research assigned to them. Each Campus unit of the IRB includes the Chair.

The Behavioral Science Committee consists of the Chair and members of the General Committee for Lankenau Campus and, in addition, two behavioral scientists and/or physicians specializing in the fields of behavioral science.

Each Campus unit of the IRB includes at least one member whose primary expertise is in a non-scientific area, and at least one member who is a physician.

The IRB has the authority to observe or have third persons observe the consent process and the research to ensure that no changes are being made to approved research.

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

When research will be reviewed involving a category of vulnerable subjects (e.g., prisoners, children, individuals institutionalized as mentally disabled), the IRB includes in its reviewing body one or more individuals, who have as a primary concern the welfare of these subjects.

B. IRB Meetings.

Scheduled meetings of the Campus General Committees are held as follows:

The Bryn Mawr Hospital Campus IRB meeting is held on the second Thursday of every month. The Lankenau Hospital Campus IRB meeting is held the fourth Monday of every month. The Paoli Memorial Hospital Campus IRB meeting is held the third Wednesday of every other month. Meeting dates may be modified periodically.

The Behavioral Committee shall meet at Lankenau Campus as needed to review studies involving human behavior.

Meetings may also be called by the Chair for an interim review at the request of any IRB member or institutional official to consider any matter concerned with the rights and welfare of any research subject.

C. IRB Meeting Preparation.

No less than ten (10) days prior to a scheduled meeting, the Institutional Review Board Coordinator (the "Coordinator") forwards to each member, or alternate member, listed on the roster, a package containing the following: all proposed protocols for initial reviews with the informed consent forms; progress reports concerning ongoing studies; amendments of approved protocols with corresponding informed consent if necessary; reports of serious and unexpected reactions and adverse reactions with corresponding informed consent forms; final reports; and other business of the Committee.

When it is determined that consultants or experts will be required to advise the IRB in its review of a protocol, the research protocol is also distributed to the consultants or experts prior to the

meeting.

Meetings are called to order by the Chair or Vice Chair and proceed according to parliamentary procedure.

The Chair coordinates and directs the agenda so that each protocol receives adequate discussion, prompts the Research Investigators for any additional information that may be needed, and promotes the exchange of opinion. He assures that all necessary and relevant matter is secured for the IRB to form sound judgment in its duty to assure the protection of the rights and welfare of humans who are to be entered into the research as subjects.

The Committee may also review research that had previously qualified for expedited review, exempt review, or emergency use. In cases where research activities were initially approved under expedited procedures and subsequently reviewed by nonexpedited procedures, the decisions reached at the convened meeting shall supersede any decisions made through the expedited review.

D. Quorum.

A quorum of a convened meeting consists of a majority of the membership of the Campus unit of the IRB for a General Committee, or their alternates, and a majority of the membership of the Behavioral Committee including two (2) behavioral scientists, or their alternates, as listed on Appendix C of the Assurance. Included in either convened Committee must be at least one (1) member physician and one (1) member whose primary expertise is in a non-scientific area.

E. 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.

Part 1, Policy II. INTRODUCTION TO THE INSTITUTIONAL REVIEW BOARD

F. Minutes.

Minutes are recorded by the Coordinator to show the following: attendance; actions taken by the Committee; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; deferrals; a written summary of the discussion of controverted issues and their resolution; if a member has a conflicting interest regarding any project, that this member did not participate in, and was not present for, the review, except to provide information requested by the IRB; and the interval designated for continuing review.

All Minutes of these Committees are maintained in the Office of Research Affairs. Condensed Minutes of these Committees are submitted to the Main Line Hospitals Board of Trustees and the Lankenau Institute for Medical Research Board of Trustees by the President of the Lankenau Institute for Medical Research. The President also submits condensed Minutes to the MEC and JCC for informational purposes.

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PAOLI HOSPITAL

BRYN MAWR REHABILITATION

RIDDLE MEMORIAL HOSPITAL

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 1

Policy No. II-B Subject:

CONFLICTS OF INTEREST: IRB MEMBERS¹ AND INVESTIGATORS²

Policy

Main Line Hospitals Institutional Review Board promotes objectivity in research by ensuring IRB Members, Investigators and research staff minimize financial conflicts of interest or even the appearance of conflicts of interest. The IRB will identify and effectively manage, or when appropriate, eliminate conflicts of interest (actual and potential) involving IRB Members and Investigators.

Definitions

1. **Conflict of Interest.** An actual or potential conflict of interest (“COI”) exists when an individual’s judgment about a matter could be biased or influenced by some other matter. Situations which involve even the appearance of a COI shall be treated as a COI under this Policy. COIs can arise whenever primary purposes (for example, the protection of human subjects or the integrity of the research) are actually or potentially in conflict with secondary purposes (for example, personal benefit or financial gain). COIs can include, but are not limited to, the following examples (whether related to the IRB Member, Investigator, or an immediate family member³ of the IRB Member or Investigator):

- Ownership or interest in a publicly traded entity sponsoring the research equal to or greater than \$10,000 or 5% of the entity’s value
- Investigator’s compensation is based on research outcome
- Ownership interest in the research agent or product which includes, but is not limited to, patent, trademark, copyright or license, or the right to royalties from commercialization
- Stocks or stock options in the research-sponsoring entity or investigational product/agent manufacturer
- Per subject or other recruitment bonuses (e.g., usually paid in addition to the negotiated research budget)
- IRB Member has an immediate family member relationship with the submitting Investigator
- IRB Member has a close personal or professional association with the submitting Investigator

¹ “IRB Members” include all IRB voting and, the Main Line Hospitals, Inc. Designated Institutional Official.

² “Investigator(s)” include the principal investigator, co-investigator, investigator staff and any other person who is responsible for the design, conduct or reporting of research which is under the jurisdiction of the IRB.

³ “Immediate family member” means: spouse, domestic partner, child (natural or adopted), step child, sibling or parent.

- IRB Member is an Investigator in the research or otherwise directly participating in the research
- A financial interest of any value in the outcome of the research
- Serves or has ever served as a board member, executive, employee, consultant, advisor or speaker for the sponsor of the research or manufacturer of the research product or agent
- Any other interest or potential interest that may negatively impact the research subject's voluntary (free from undue influence) and informed choice to participate in the research

2. **Covered Persons.** This Policy applies to the following individuals (“Covered Persons”):

- IRB Members (as defined in footnote 1 of this Policy)
- Investigators (as defined in footnote 2 of this Policy)
- Immediate family member (as defined in footnote 3 of this Policy)

Disclosure

Each Covered Person shall disclose to the Director of Regulatory Affairs (“Director”) all COIs using either Form “A” (for IRB Members) or Form “B” (for Investigators). COI Disclosure Forms shall be submitted by IRB Members annually. Investigators shall submit the appropriate COI Disclosure Form with each new research study and update each such COI Disclosure Form annually. For all Covered Persons, whenever there is a change in circumstances which would render an earlier disclosure untrue or incomplete, the Covered Person shall promptly submit a new COI Disclosure Form (Form A or Form B, as applicable).

Evaluation and Resolution or Management of Conflicts of Interest

The Chair of the IRB (“Chair”) and Director shall be responsible for reviewing COI Disclosure Forms and identifying, addressing and resolving/managing actual or potential COIs. Actual or potential COIs involving the Chair or Director shall be addressed and resolved/managed by the other (either the Chair or Director) and the Main Line Health Designated Institutional Official. The goal of conflict evaluation and resolution or management is to mitigate the COI.

Whenever a matter comes before a meeting of the IRB where an IRB Member has a COI and is present for the meeting, the IRB Member must acknowledge the COI and may not be counted as present in determining a quorum for the matter to be decided. As requested by the IRB, the IRB Member with the COI may provide information and answer pertinent questions but shall not participate in the deliberation of the matter or vote. At the discretion of the IRB Chair, the IRB Member with the COI may be present throughout the presentation of information related to the matter. The minutes of the IRB meeting should reflect that a COI existed and the manner of its management (e.g., the IRB Member provided information but was excused from the meeting for deliberation and vote).

IRB submissions (for initial and continuing IRB review) shall include a Form “B” for all research personnel meeting the definition of Investigators.

Nothing in this Policy shall limit the range of options available to the IRB, Chair or Director (or Designated Institutional Official) in eliminating, resolving or managing COIs. The IRB shall function in an independent and unbiased manner, free from even the appearance of a COI. The IRB shall not approve (or reapprove) research activity which the IRB believes to be the subject of a COI or the appearance of a COI.

Education and Training

Covered Persons shall participate in education and training activities as determined by the Office of Research Affairs (IRB Office) related to recognizing and disclosing COIs.

Documentation

All COI and related documents will be maintained in the Office of Research Affairs

Regulatory References

PHS Regulations: 42 CFR 50 Subpart F Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is sought

FDA Regulations: 21 CFR 54 Financial Disclosure by Clinical Investigators

HHS Regulations 45 CFR 46 Protection of Human Subjects 46.107(e) **Revision**

Date

08/17/2009

BRYN MAWR HOSPITAL

LANKENAU HOSPITAL

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LANKENAU INSTITUTE FOR MEDICAL RESEARCH

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 1

Policy No. III.

Subject: RESEARCH DETERMINATION

A. Research vs. Innovative Practice

The distinction between research and innovative practice in patient care is important regarding IRB jurisdiction and should be based on the following considerations:

1. 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.
2. Care of a patient is considered innovative practice if there is no research intent when the patient care will entail using innovative treatment, and there will be no collection of data at any time for any research purpose.

B. Humans As Subjects In Research

1. A human subject is defined as a living human being from whom a Research Investigator obtains data through intervention or interaction with the subject or obtains identifiable private information.
2. The Chair, in consultation with Research Investigators and department heads, makes a determination as to whether research will involve human subjects as defined in 45 CFR 46.102 or 21 CFR 56.102.

C. Special Administrative/Executive Preview and Opportunity for Comment.

The Director of Regulatory Affairs in cooperation with the Chair will act upon receipt of a proposed research study which presents novel, unusual or controversial issues (as determined by them alone or in consultation with the President of LIMR, CEO of Main Line Health, institutional officials, department officials, advisors, or the Chair of the MEC), as follows:

1. Refer such research study to the appropriate Institutional Administrative and/or Executive body(ies) for preview and comment.
3. Withhold submission to the IRB until such time as the above preview and comment is completed.

Part 1, Policy III. RESEARCH DETERMINATION

3. Not submit the proposed study to the IRB if, after the Administrative/Executive preview, the President of LIMR, CEO Main Line Health, MEC or JCC or Board of Trustees disapproves the research study, thereby making it ineligible for IRB review.

Note: For purposes of this section, the terms novel, unusual or controversial “issues” include without limitation, studies presenting significant additional costs to the Institution, or proposed studies with very high risk or having other features or aspects which would be contrary to its operations, institutional policies or community trust.

D. When IRB Review is Required.

1. Rule. All research must be submitted to the Office of Research Affairs for a determination of review status by the Director in cooperation with the Chair; all research must be reviewed by the IRB if the following conditions apply:
 - a. The research involves “human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the [HHS] policy applicable to such research.” (45 CFR 46.101)
 - b. The research involves “clinical investigations regulated by the FDA, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.” (21 CFR 50.1)
2. Type of Review. The Director in cooperation with the Chair determines the type of review process (full, expedited, exempt, waiver) upon receipt of the research study and then in writing notifies the Research Investigator of this determination. (See Section for Office Use, Protocol Submission Form.) The Director in cooperation with the Chair shall refer all non-exempt research protocols to either full committee review or expedited review.

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 1

Policy No. IV.

Subject: APPLICATION - INSTITUTIONAL REVIEW BOARD PROCESS

The Committee expects that the Research Investigator planning the research, in collaboration with the appropriate department head and Institution officials, will review the responsibilities outlined in the Assurance.

A. Research Investigator's Obligations: Procedure for Submitting a New Research Protocol.

1. Research Investigators submitting a new research protocol, must contact the Office of Regulatory Affairs to obtain the appropriate forms and submission instructions for first time review.
 - a. the IRB Coordinator will provide the appropriate forms and instructions for the type of submission.
2. The Research Investigator must complete the appropriate materials supplied by the Coordinator. These materials are required for administrative purposes and form the basis for the IRB's risk/benefit determination.

B. Procedure for Delivering the Protocol.

1. The Research Investigator must submit eighteen (18) packets to the ORA which include copies of the complete protocol, informed consent form, Forms 001 and 002, and any materials which require review/approval by the IRB.

C. The IRB's Obligations: Procedure Upon Receipt of the Protocol.

1. Upon receipt of the protocol, the IRB Coordinator determines the location of review based on the request for approval as outlined on Form 001.
2. The Coordinator places the protocol on the agenda of the next scheduled IRB meeting at the appropriate Campus and assigns a specific time allotment for the Research Investigator to present the protocol. Questions or requests for further information may be directed to the Coordinator at 610-645-2692.

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
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Part 1

Policy No. V.

Subject: FULL COMMITTEE REVIEW PROCESS

A. Committee Preparation.

A new protocol is assigned to two members of the committee (primary reviewers) by the Director of Regulatory Affairs in cooperation with the Chairperson of the MLH IRB for their analysis at the meeting of the IRB. Preferably, at least one of the reviewers will be knowledgeable in the field of the research study described in the protocol. The primary reviewers receive the appropriate MLH internal forms, the complete protocol, the informed consent, and the investigator's brochure/manual, if available. If the study is included in a grant application to either a government agency or a private foundation, a copy of the grant is also included for review. The primary reviewers present their in-depth analysis of the protocol and informed consent to the committee. The other members of the committee are expected to read the internal forms, protocol, and informed consent and participate in the review of the protocol after the primary reviewers have completed their presentations. The members receive the protocol and associated materials from the IRB Coordinator no less than 10 days prior to the meeting. When it is determined by the Director in cooperation with the Chairperson of the MLH IRB that consultants or experts will be required to advise the IRB in its review of the protocol, the research protocol and associated materials are also distributed to the consultant(s) or expert(s) no less than 10 days prior to the meeting. At the assigned meeting, the protocol shall be presented by the Research Investigator or representative according to the agenda.

B. Approval Criteria.

Criteria used by the IRB to determine initial approval, as well as, continuing approval, include but may not necessarily be limited to the following:

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; and

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Part 1, Policy V. FULL COMMITTEE REVIEW PROCESS

2. risks to subjects are reasonable in relation to anticipated benefits and the importance of the knowledge that may be expected to result from their participation; and
3. selection of subjects is equitable; and
4. informed consent will be sought from each prospective 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, if applicable, and will be adequate and accurate; and
5. informed consent will be appropriately documented in accordance with and to the extent required by 45 CFR 46.117 and 21CFR 50.27, if applicable; and
6. where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects; and
7. where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and
8. appropriate additional safeguards have been included to protect the rights and welfare of subjects vulnerable to coercion or undue influence.

C. Committee Action During the Meeting

1. The Principal Investigator presents the protocol to the Board.
2. The Committee members present their questions and concerns regarding the research to the Principal Investigator or his/her representative. At the conclusion of the questions and discussion with the Principal Investigator, the Principal Investigator is excused from the meeting.
3. The assigned reviewers present their analysis of the protocol and informed consent followed by discussion by the entire Committee.
4. The Committee determines the interval for continuing review that is appropriate to the degree of risk/benefit to the subjects. In no event may the interval for review exceed twelve (12) months.
5. After the discussion by the Committee, the Committee votes to approve, approve with modifications, defer, or disapprove the research protocol. The decision is determined by a simple majority vote.
6. The Committee specifies any modifications to a protocol or informed consent that it may require so that the study may be granted final approval.
7. The Committee specifies its reasons for disapproving a study.
8. The Committee specifies its reasons for deferring to vote on a study.

D. Procedures for the Chair.

1. Call the meeting to order and proceed according to parliamentary procedure allowing full opportunity for adequate discussion.
2. Receive the decision of the Committee and the interval established for continuing review of the approved research.

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 1

Policy No. VI.

Subject: EXPEDITED REVIEW PROCESS

This is a procedure through which the Chair, or designee who is also an IRB member, 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 full IRB.

Rule. The Director of Regulatory Affairs in cooperation with the Chair or designee determines whether the research study meets the criteria necessary for an expedited review process. Use of this procedure does not allow disapproval of the research by the reviewer. The expedited review process may be used to review either or both of the following:

A. Minor Changes to Previously Approved Research.

Revisions (minor changes) are being made in previously approved research during the period of one year or less for which approval is authorized by the IRB. Examples: editorial (study title, pagination), administrative (change of telephone number of contact person).

1. Procedure for the Research Investigator. The Research Investigator must submit three copies of Form 001 which should reflect the revisions being made in the report section, accompanied by the appropriate materials from the study sponsor. The protocol and/or consent form must be included if affected by the revisions.
2. Procedure for the Office of Research Affairs and Chair/Designee.
 - a. Make the determination that the submitted materials qualify for expedited review.
 - b. Forward copies to select members of the IRB as designated by the Chair for review.
 - c. Follow up with assigned reviewers and receive comments.
 - d. Following determination, notify Investigator of action taken or to be taken.
 - e. Refer any research study which the reviewer disapproved to the full Committee for review.
 - f. Inform the IRB of expedited research studies which have been approved. g. Maintain records of foregoing activities.

3. Committee Action. Any member at a convened meeting may request that an activity which has been found to meet the expedited review criteria be reviewed by the IRB in accordance with non-expedited procedures. A vote of the members is taken concerning the request and the majority decides the issue.

B. Minimal Risks

1. The research involves no more than “minimal risk” (see Glossary) to human subjects and involves only procedures listed in one or more of the following categories:
 - a. clinical studies of drugs and medical devices only when condition (1) or (2) is met:
 - 1) 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.)
 - 2) research on medical devices for which an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and the device is being used in accordance with its cleared/approved labeling.
 - b. collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
 - 1) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amount drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week
 - 2) from adults and children, considering the age, weight, and health of the subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
 - c. prospective collection of biological specimens for research purposes by non-invasive means. Example:
 - 1) hair and nail clippings in a nondisfiguring manner;
 - 2) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;
 - 3) permanent teeth if routine patient care indicates a need for extraction.
 - 4) excreta and external secretions including sweat;

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- 5) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;
 - 6) placenta removed at delivery;
 - 7) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
 - 8) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the procedure is accomplished in accordance with accepted prophylactic techniques;
 - 9) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;
 - 10) sputum collected after saline mist nebulization.
- d. 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:
- 1) 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.
 - 2) weighing or testing sensory acuity,
 - 3) magnetic resonance imaging;
 - 4) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow and echocardiography;
 - 5) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- e. research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
- f. collection of data from voice, video, digital, or image recordings made for research purposes.

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD****Part 1****Policy No. VII.****Subject: EMERGENCY USE PROCESS**

Under certain circumstances a physician may provide emergency medical care using an unapproved investigational drug, device or biologic. This use requires an Investigational New Drug ("IND") or Investigational Device Exemption ("IDE") and is meant for a single patient outside of an ongoing clinical trial. That is, the intended subject does not meet the criteria of an existing study protocol, or an approved study protocol does not exist.

This use, by its nature, prevents the review process established by this Institution for approving the use of investigational drugs, devices, or biologicals from happening, and may rarely be expected to apply. However, nothing in these procedures is intended to limit the authority of a physician to provide emergency medical care for the patients except as provided by law.

A physician may obtain an Emergency IND or IDE and administer a test article, without first obtaining prospective IRB review and approval, only under the strict rule below. (See 21 CFR 50.23, 56.102(d) and 56.104(c))

A. The strict rule for "emergency use" is as follows:

1. In the event of an unforeseeable emergency, use of an investigational drug, device, or biologic product may be exempt from FDA requirements for IRB review provided that:
 - a. the patient is in a life-threatening situation that needs immediate treatment;
 - b. in which no standard acceptable treatment is available; and c. in which there is not sufficient time to obtain IRB approval.
2. The provision for emergency use would almost never apply to a treatment protocol (IND) because such use is planned and sufficient time is available to obtain IRB review and approval.
3. Data may not be collected or used in any analysis at any time during or after the emergency use of the test article. The patient may not be considered to be a research subject.

Part 1, Policy VII. EMERGENCY USE PROCESS

4. Any subsequent use of the investigational product at the Institution is subject to full IRB review. (Note: the FDA believes it inappropriate to deny emergency treatment when the only obstacle is lack of time for the IRB to convene, review and give approval. FDA Information Sheets at page 52, September 1998)

B. Procedure for the Physician.

1. Notify the ORA by telephone about the intended use. This notification is necessary to begin tracking of the emergency use as required by law and shall not be construed as IRB approval.
2. Before use of the test article, obtain informed consent of the subject or the subject's legally authorized representative/Surrogate unless both the Research Investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all the following:
 - a. the subject is confronted by a life-threatening situation necessitating the use of the test article, and
 - b. informed consent cannot be obtained because of an inability to communicate with the subject or obtain legally effective consent, and
 - c. time is not sufficient to obtain consent from the subject's legal representative/Surrogate, and
 - d. no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the life of the subject.
3. If, in the Research 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 Research 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. (See 21 CFR 50.23 (b))
4. Forward a copy of the signed informed consent to the ORA.
5. Submit a written report - including the documentation required in paragraphs 2, 3 and 4 of this section - of the emergency use and the situation requiring same to the ORA within five (5) working days after the use of the test article. (See 21 CFR 50.23 (c))
6. Notify the sponsor of the emergency use if an IND and IDE exists, or the FDA directly if no IND or IDE exists.

INFORMATION SHEETS**Guidance for Institutional Review Boards and Clinical Investigators
1998 Update**

**"Off-Label" and Investigational Use
Of Marketed Drugs, Biologics, and Medical Devices****"Off-Label" Use of Marketed Drugs, Biologics and Medical Devices**

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

Investigational Use of Marketed Drugs, Biologics and Medical Devices

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

- (i) 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;
- (ii) it is not intended to support a significant change in the advertising for the product;
- (iii) 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;
- (iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
- (v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
- (vi) it does not intend to invoke 21 CFR 50.24.

For additional information on whether or not an IND or IDE is required in a specific situation, contact:

For DRUG PRODUCTS contact: Drug
Information Branch (HFD-210) Center for
Drug Evaluation and Research Food and
Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
301-827-4573

For a BIOLOGICAL BLOOD product, contact:
Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
301-827-3518

For a BIOLOGICAL VACCINE product, contact:
Office of Vaccines Research and Review (HFM-400)
Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892-0001
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:
Office of Therapeutics Research and Review (HFM-500)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1420
301-594-2860

For a MEDICAL DEVICE product, contact:
Program Operations Staff (HFZ-403)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850
301-594-1190

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD****Part 1****Policy No. VIII.****Subject: SINGLE PATIENT USE PROCESS (formerly, “compassionate use”)**

There has been considerable confusion on the part of Research Investigators, as well as the IRB, as to “compassionate use” and “emergency use”. The term “compassionate use” has formerly been used to refer to the provision of investigational drugs outside of an ongoing clinical trial to a limited number of patients who are desperately ill and for whom no standard alternative therapies are available. The term does not appear in FDA or DHHS regulations. Single patient use allows a physician to obtain access to an investigational drug, device, or biological product for the treatment of a single patient only. Usually the patient is in a desperate situation and unresponsive to other therapies, or in a situation where no approved or generally recognized treatment is available. Further, there is usually little evidence that the proposed therapy is useful, but may be plausible on theoretical grounds or anecdotes of success.

Rule. Prospective IRB approval under the full review process is required since this is a planned use.

A. Access to Test Article. Access to a test article for use on a single patient may be gained as follows:

1. through the sponsor by contacting the sponsor and requesting permission to administer the test article under a treatment protocol, or if permission is not granted or no IND exists,
2. through the FDA by first obtaining the test article from the sponsor, and then submitting a treatment IND to the FDA requesting authorization to use the article for treatment use. (21 CFR 312.35)

Part 1, Policy VII. SINGLE PATIENT USE PROCESS (formerly, "compassionate use")

B. Procedure for the Research Investigator.

Submit to the ORA a Protocol Submission Form (Form 001), entering the test article name, sponsor, and IND#; also, submit a single typewritten page narrative describing the circumstances under which the test article is to be used. Include a copy of the protocol and informed consent to be used, and the sponsor's Research Investigator's Brochure, if available. Construction of the consent should be made according to the format in the form, Informed Consent Requirements or as provided by the ORA.

1. If the use is approved by the IRB, proceed to obtain informed consent.
2. Forward a copy of the signed informed consent (may be faxed) to the ORA before the test article is administered.

C. Procedure for the Chair. Process under full review procedures, Section IV.

D. Procedure for the Committee. Process the application according to full IRB review procedures. (See Section IV)

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD****Part 1****Policy No. IX.****Subject: TREATMENT IND PROCESS (Investigational New Drug)**

This use of a test article is made available by the FDA for promising new drugs as follows:

“A treatment IND is a treatment protocol that is added to an existing investigational new drug application (IND), which allows physicians to treat qualifying patients according to the protocol, and which provides additional data on the drug’s safety and effectiveness. Treatment INDs are available for patients with life-threatening or other serious diseases for which no satisfactory alternative drug or other therapy exists.” (See 21 CFR 312.34) Treatment INDs may be available when the trial sponsor is actively pursuing marketing approval.

Rules for use. Prospective IRB approval under full Committee review is required since this is a planned use of a test article.

- There are no limitations to the number of subjects who may be entered.
 - The test article may be used only in accordance with the plan of investigation described in the protocol;
 - The test article may be used only in subjects under the Research Investigator’s personal supervision or under the supervision of other Research Investigators who are responsible to him or her;
 - Informed consent must be obtained from subjects in the study.
- A. Procedure for Research Investigator. Obtain submission guidance from the ORA. Complete a Protocol Submission Form (Form 001) to include a description of the test article and it’s intended use, IND#, study sponsor, protocol and informed consent form.
- B. Procedure for the Chair Process the application under full IRB review procedures, Section IV.
- C. Procedure for Committee. Review the application according to full IRB review procedures, Section IV.

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Part 1

Policy No. X.

Subject: TREATMENT IDE PROCESS (Investigational Device Exemption)

Treatment use of a test article is made available by the FDA for promising new devices according to the following provisions:

“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 a treatment investigational device exemption (IDE).” (See 21CFR812.36)

The regulations for the treatment use of investigational devices are intended “to facilitate 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.” Two conditions are specified as follows:

- 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.

Definitions according to use herein:

- “Treatment use” of a device includes the use of a device for diagnostic purposes.
- “Immediately life-threatening disease” means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.
- “Investigator” is a licensed practitioner who receives a investigational device for treatment use under a treatment IDE and is responsible for meeting all applicable investigator responsibilities under part 812.36 and parts 50 and 56 of chapter 21.

Part 1, Policy X. TREATMENT IDE PROCESS (Investigational Device Exemption)

Criteria for use. FDA shall consider the use of an investigational device under a treatment IDE if:

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 or other therapy available to treat or diagnose that stage of 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 such clinical trials have been completed; and
4. The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence.

Rules for use. Prospective IRB approval under full Committee review is required since this is a planned use of a test article.

1. There are no limitations to the number of the subjects who may be entered.
2. The test article may be used only in accordance with the plan of investigation described in the protocol;
3. The test article may be used only in subjects under the Research Investigator's personal supervision or under the supervision of other Research Investigators who are responsible to him or her; and
4. Informed consent must be obtained from subjects in the study.

A. Procedure for Research Investigator.

1. Obtain FDA approval for use of the investigational device under a treatment IDE.
2. Obtain the appropriate materials from the ORA and submit a description of the use of the investigational device, the protocol, informed consent form, sponsor's name, address, and telephone number.

B. Procedure for the Chair.

1. Process the application under full IRB review procedures, Section IV.

C. Procedure for the Committee.

1. Determine risk, significant/non-significant, according to Section XVI.
2. Review under full IRB review procedures, Section IV.

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Part 1

Policy No. XI.

Subject: PARALLEL TRACK PROCESS

The FDA's Parallel Track policy (57 FR 13250) permits wider access to promising new drugs for AIDS and HIV-related diseases under a separate "treatment" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating acquired immunodeficiency syndrome (AIDS) and other HIV-related diseases.

Rules for use. Prospective IRB approval under full review process is required.

- The test article may be used only in accordance with the plan of investigation described in the protocol;
 - The test article may be used only in subjects under the Research Investigator's personal supervision or under the supervision of other Research Investigators who are responsible to him or her;
 - Informed consent must be obtained from subjects in the study.
- A. Procedure for Research Investigator. Obtain the appropriate materials from the ORA and submit a description of the use which should include the test article, IND#, and sponsor, as well as the protocol and informed consent.
- B. Procedure for Committee. Process the application according to full IRB review procedures. (See Section IV)

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Part 1

Policy No. XII.

Subject: EXEMPT INSTITUTIONAL REVIEW BOARD PROCESS

Rule. Research which may qualify for exemption under 45 CFR 46.101 (b) (exemption from the requirement that research first be reviewed and approved by the IRB) must first be reported to the ORA for both confirmation of this determination before it may be initiated.

Research Investigators do not have the right to make an independent determination that research involving human subjects is exempt.

A. Procedure for Research Investigator: Submit a copy of the *Protocol Submission Form* with the proposed research study in letter form to the ORA.

B. Procedure for the ORA:

1. Review proposed 'exempt' research in cooperation with the Chair and in consultation with IRB members if deemed necessary and send written Notice of Determination to Research Investigator to confirm exempt status.
2. Notify the Research Investigator in a letter signed by either the Director or the Chair as to whether the research is exempt from IRB review.
3. Forward to HHS all exempted research protocols approved by the IRB which are being submitted for HHS funding.
4. Maintain records of foregoing activities.

C. HHS and FDA Exemptions. Certain specifically exempted categories of research under HHS and FDA regulations are as follows:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Part 1, Policy XII. EXEMPT INSTITUTIONAL REVIEW BOARD PROCESS

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude,

- achievement), survey procedures, or observation of public behavior, unless:
- (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - (ii) disclosure of the human subjects' responses outside the research could reasonably place the subject at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior is not exempt under paragraph (2) of this section if:
- (i) the human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the Research Investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
- (i) public benefit or service programs;
 - (ii) procedures for obtaining benefits or services under those programs or procedures; or
 - (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.
6. Taste and food quality evaluation and consumer acceptance studies if: (i)
- 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 or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 1

Policy No. XIII.

Subject: WAIVER OF IRB REVIEW

On the application of a sponsor or sponsor - investigator, the FDA may waive any of the requirements contained in the IRB regulations, including the requirements for IRB review, for specific research activities, or for classes of research activities otherwise covered by the IRB regulations. (See 21 CFR 56.105)

FDA anticipates using this waiver provision only in very special circumstances, where it would be in the best interest of the subjects and where alternative mechanisms for assuring the protection of the subjects is adequate. Waiver may apply to treatment INDs but is inappropriate for emergency use situations because IRB review is already exempted.

Rule. Research activities that have been granted a waiver from IRB review by the FDA must still be submitted to the IRB for determination. Such waiver does not apply to informed consent requirements.

A. Procedure for the sponsor or sponsor-investigator.

1. Submit a request for a waiver associated with a "treatment IND" to the Division in the Center for Drug Evaluation and Research (CDER) or to the Division in the Center for Biologic Evaluation and Research (CBER) responsible for reviewing the IND.

B. Procedure for Research Investigator.

1. If a waiver is granted by the FDA, obtain the appropriate materials from the ORA. These materials should be submitted along with a specific request for the waiver of IRB review as well as a complete protocol and informed consent.

2. If the waiver is acceptable to the ORA and the Chair, proceed to obtain informed consent from the subject before the test article is administered. Forward copy to the ORA.

3. If full IRB review is required, proceed according to section IV.

Part 1, Policy XIII. WAIVER OF IRB REVIEW

C. Procedures for the ORA.

1. Determine in cooperation with the Chair whether the study is appropriate for the waiver exemption from IRB review. Notify the investigator in a letter signed by the Chair as soon as practicable of determination as to waiver of IRB review or requirement of full review.
2. For waiver of IRB review, maintain a copy of the waived protocol. A letter signed by the Chair describing the action taken will be forwarded to the investigator.
 - a. Receive and file copy of the signed consent form.
 - b. Report action to the Committee.
3. For full review, proceed as in section IV.
4. Maintain records of the foregoing activities in the Office of Research Affairs.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**Part 1****Policy No. XIV.****Subject: INFORMED CONSENT DOCUMENTATION**

Rule. In accordance with 45 CFR 46.117 and 21 CFR 50.27, 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 subject's legally authorized representative/Surrogate at the time consent is given. A signed copy must be given to the person signing the form. It is the absolute responsibility of the Research Investigator to obtain informed consent from the research participant unless a specific exemption applies.

A. Documentation of informed consent. Except as provided in 21 CFR 56.109 (c) (having to do with "minimal risk" and emergency research), the consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent (see below) required by 45 CFR 46.116 and 21 CFR 50.25. This form may be read to the subject or the subject's legally authorized representative/Surrogate, but, in any event, the Research Investigator must give either the subject or the representative/Surrogate adequate opportunity to read it before it is signed and dated.
2. A "short form" written consent document stating that the elements of informed consent required by 21 CFR 50.25, 45 CFR 46.116 has been presented orally to the subject or the subject's legally authorized representative/Surrogate. 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 representative/Surrogate. Only the short form itself is to be signed by the subject or the representative/Surrogate. However, the witness must sign both the short form and a copy of the summary. A copy of the summary must be given to the subject or the representative/Surrogate in addition to a copy of the short form.
 - For potential subjects who do not speak English, where informed consent is documented using the short form procedure, the written informed consent must contain, in language understandable to the subject, all the elements necessary for legally effective informed consent.
 - (i) The oral presentation and the short form written informed consent document must be in a language understandable to the subject;
Hospital translator services must be used.

(ii) The IRB-approved English language informed consent document may serve as a summary; and

(iii) The witness must be fluent in both English and the language of the subject
The translator/interpreter may act as the witness

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 convened IRB.

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.

B. Basic Elements of Informed Consent. (see *GUIDELINES*) In seeking informed consent, the following information must be provided to each subject:

1. A statement that the study involves research and the expected duration of the subject's participation, a description of the procedures to be followed, and an identification of any procedures which 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 which 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 that notes the possibility that the FDA may inspect the records if FDA regulated products are involved. For all studies, indicate that OHRP 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.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

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

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) which are currently unforeseeable.

2. Anticipated circumstances under which the subject's participation may be terminated by the Research Investigator without regard to the subject'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 which 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.

D. Waiver of Signed Consent Form Requirement. The IRB may waive, on a case by case basis, the requirement that the Research Investigator obtain a signed consent form for some or all subjects if the IRB determines that:

1. the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern; or
2. 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.
3. in cases where the requirement for signed informed consent has been waived, the IRB shall maintain a record of such waiver in the ORA and may require the Research Investigator to provide subjects with a written statement regarding the research.

E. Use of Facsimile, Mail or Telephone to Document Informed Consent

The IRB may approve a process that allows the informed consent document to be delivered by telephone, mail or facsimile to the subject or LAR, and to conduct the consent interview by telephone. On a case by case basis, the IRB may require that the subject or the LAR can read the consent document as it is discussed. All other applicable conditions and waivers for documentation of informed consent must be met when using this procedure.

F. Procedure for the Research Investigator.

1. Model the informed consent form according to the format in the *Informed Consent Requirements* form within the *GUIDELINES*.
2. Obtain informed consent from the research subject as set forth herein.
3. Maintain signed consent documents as required by the federal regulations. (See 21 CFR 312.62 and 45 CFR 46.115)

G. Procedure for the Committee.

1. Review the proposed informed consent form for completeness according to the *GUIDELINES*.
2. Require that information provided to subjects as part of informed consent is in accordance with the aforementioned 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.

**PART 1, POLICY
XIII REVISED
12/2009**

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Part 1

Policy No. XV.

Subject: WAIVER OR ALTERATION OF INFORMED CONSENT PROCESS

Rule. In studies not regulated by the FDA, the IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in 45 CFR 46.116 (a) and (b), or waive the requirements to obtain informed consent under 46.116 (c) if it finds and documents that:

1. 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:
 - a. Programs under the Social Security Act, or other public benefit or service programs;
 - b. Procedures for obtaining benefits or services under these programs;
 - c. Possible changes in or alternatives to those programs or procedures;
 - d. Possible changes in method or levels of payment for benefits of services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

Rule. The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in 45 CFR 46.116 (a) and (b), or waive the requirements to obtain informed consent, 46.116 (d), provided the IRB finds and documents that:

1. the research involves no more than minimal risk to the subjects;
2. the waiver or alteration will not adversely affect the right and welfare of the subjects;
3. the research could not practicably be carried out without the waiver or alteration; and
4. whenever appropriate the subjects will be provided with additional pertinent information after participation.

IRB Action. When the documentation requirement is waived, the IRB shall require the Research Investigator to provide subjects with a written statement regarding the research.

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Part 1

Policy No. XVI.

Subject: EMERGENCY RESEARCH CONSENT WAIVER. (See 21 CFR 50.24)

Rule. The IRB may approve research without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not a participant in the research) finds and documents each of the following:

1. the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled trials, is necessary to determine the safety and effectiveness of particular interventions.
2. obtaining informed consent is not feasible because:
 - a. the subjects will not be able to give their informed consent as a result of their medical condition;
 - b. the intervention under investigation must be administered before consent from the subjects' legally authorized representative/ Surrogate is feasible; and
 - c. there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research.
3. participation in the research holds out the prospect of direct benefit to the subject because:
 - a. subjects are facing a life-threatening situation that necessitates intervention;
 - b. appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - c. risks associated with the investigation 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, if any, and what is known about the risks and benefits of the proposed intervention or activity.
4. the research could not practicably be carried out without the waiver.
5. the protocol defines the length of the potential therapeutic window based on scientific evidence.

A. Procedure for the Committee.

1. The IRB must review and approve informed consent procedures and an informed consent document consistent with 21 CFR 50.25 or 45 CFR 46.116 and 46.117 if research is not subject to FDA regulations. These informed consent procedures and documents must be used with subjects or their legally authorized representative/Surrogate where use of such procedures and documents is feasible.
2. The IRB must review and approve the procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the research. The IRB shall further obtain a commitment from the Research Investigator to attempt to contact, within the therapeutic window, the subject's family member who is not a legally authorized representative/Surrogate, and offer such family member an opportunity to object to the subject's participation in the research.
3. The IRB must have a dialogue with representatives of the communities in which the research will be conducted and from which the subjects will be drawn.
4. The IRB will make public disclosure to the communities in which the research will be conducted and from which the subjects will be drawn, prior to the initiation of the research, of plans for the research and its risks and expected benefits.
5. The IRB will make public disclosure to the communities outlined in 4. above, of sufficient information following completion of the research to appraise the communities and the researchers of the study, including the demographic characteristics of the research population and its results.
6. The IRB shall establish an independent data monitoring committee to exercise oversight of the research.
7. The IRB shall ensure that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject is incapacitated or unavailable, a legally authorized representative//Surrogate, or if a legally authorized representative/Surrogate is not reasonably available, a family member, of the subject's inclusion in the research, the details of the research and other information contained in the informed consent document, including but not limited to the right to discontinue the subject's participation at any time without penalty or loss of benefits.
8. The IRB must document and retain for at least three years following the completion of the research all determinations required by this Section XIV.
9. If the IRB determines that it cannot approve a research proposal because the research does not meet the criteria in the exception (set forth in 21 CFR 50.24 (a)) or because of other relevant ethical concerns, the IRB must document its findings and provide them promptly, in writing, to the Research Investigator and the sponsor of the research.
10. Where the research is not subject to FDA regulations, the IRB must report to the OHRP that the determinations, commitments and procedures required by this Section XIV have been met. (See OHRP Reports No. 97-01, 10/31/96; 61 FR 51531, 10/2/96)

B. Procedure for the Research Investigator.

1. Obtain a separate IND (“investigational new drug”) application or IDE (“investigational device exemption”) that clearly identifies the research protocol as a protocol that may include subjects who are unable to consent. Proof of such IND application or IDE must be provided to the Chair before the protocol is submitted to the IRB for review. (Submission of the protocol in a separate IND/IDE is required even if an IND for the same drug or an IDE for the same device already exists.)
2. Submit appropriate protocol and informed consent material to the IRB in accordance with Sections III and XII of these Procedures.
3. Commit to attempt to contact a legally authorized representative/Surrogate of each subject within the therapeutic window, and if feasible, ask the legally authorized representative/Surrogate/Surrogate to consent within that window rather than proceeding without consent. The Research Investigator must summarize efforts made to contact legally authorized representative/Surrogate/Surrogates and make the information available to the IRB, in writing, at the time of continuing review.
4. Commit that if obtaining the subject’s informed consent is not feasible and a legally authorized representative/Surrogate is not reasonably available, the Research Investigator will, if feasible, within the therapeutic window, attempt to contact the subject’s family member and ask whether he or she objects to the subject’s participation in the research. The Research Investigator must summarize efforts made to contact a family member and make the information available to the IRB, in writing, at the time of continuing review.
5. Commit to inform, at the earliest feasible opportunity, each subject, or if the subject is incapacitated or unavailable, a legally authorized representative/Surrogate, or if a legally authorized representative/Surrogate is not reasonably available, a family member, of the subject’s inclusion in the research, the details of the research and other information contained in the informed consent document, including but not limited to the right to discontinue the subject’s participation at any time without penalty or loss of benefits.
6. Commit to inform as soon as feasible, the subject, if the subject’s condition improves and the legally authorized representative/Surrogate or family member was told about the research.
7. If subject is entered into research with waived consent and the subject dies before the legally authorized representative/Surrogate or family member can be contacted, information about the research is to be provided to the legal representative or family member, if feasible. The Research Investigator must summarize efforts made to disclose the subject’s participation in the research to the subject, legally authorized representative/Surrogate or family member, as set forth above, and make the information available to the IRB, in writing at the time of continuing review.
8. Participate in the community dialogue process as required by the Chair.

D. Procedures for the Chair and ORA.

1. Process under full review procedures, Section IV.
2. Assure compliance with special regulations concerning IRB responsibilities in approving

Emergency Research Waiver.

3. Comply with special reporting requirements as required by OHRP.

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Part 1

Policy No. XVII.

Subject: SIGNIFICANT RISK/NONSIGNIFICANT RISK DEVICE DETERMINATION

An Investigational Device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety data of the device. Such clinical investigations must be conducted according to the requirements of the IDE regulations (21 CFR part 812). Unless exempt from the IDE regulations, an investigational device must be categorized as either "significant risk" (SR) or "nonsignificant risk" (NSR). The determination that a device presents a nonsignificant risk or significant risk is initially made by the sponsor. The proposed study is then submitted to the FDA (for SR studies) or to an IRB (for NSR studies).

- A. Significant risk device. A significant risk device study presents a potential for serious risk to the health, safety, or welfare of a subject and
1. is an implant; or
 2. is used in supporting or sustaining human life; or
 3. is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
 4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- B. A nonsignificant risk device study does not meet the definition of a significant risk study.

The sponsor, usually through the clinical Research Investigator, provides the IRB with information necessary to make a determination as to risk.

If the IRB agrees that the device study is NSR and approves the study, the research may begin at the Institution immediately without submission of an IDE application to FDA.

If the IRB believes that a device study is SR, the research may not begin until both the IRB and FDA approve the investigation. The IRB notifies the investigator and where appropriate the sponsor who must notify the FDA of the determination. (21 CFR 812.66)

Part 1, Policy XVII. SIGNIFICANT RISK/NONSIGNIFICANT RISK DEVICE DETERMINATION

Rule. Once the final SR/NSR decision has been rendered by the IRB (or FDA) the IRB determines the type of review required and proceeds as with any other study. Both SR and NSR studies require prospective IRB approval.

- Some NSR studies may qualify as “minimal risk” studies, and thus, may qualify for expedited review.
- SR studies require full review.

INFORMATION SHEETS
Guidance for Institutional Review Boards and Clinical Investigators
1998 Update

Significant Risk and Nonsignificant Risk Medical Device Studies

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR). An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure. For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

Distinguishing Between SR and NSR Device Studies

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA.

If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

SR/NSR Studies and the IRBThe NSR/SR Decision

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. 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 should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. Two examples follow:

The study of a pacemaker that is a modification of a commercially--available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.

The study of an extended wear contact lens is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE

with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

IRB and Sponsor Responsibilities Following SR/NSR Determination

If the IRB decides the study is Significant Risk:

1. IRB Responsibilities:

Notify sponsor and investigator of SR decision

After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

2. Sponsor Responsibilities:

Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination; Study may not begin until FDA approves IDE and IRB approves the study. Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

If the IRB decides the study is Nonsignificant Risk:

1. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]

2. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR

studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

Examples of NSR/SR Devices

The following examples are provided to assist sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical devices. Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

NONSIGNIFICANT RISK DEVICES

Low Power Lasers for treatment of pain
Caries Removal Solution
Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
Conventional Gastroenterology and Urology Endoscopes and/or Accessories
Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)
Conventional Implantable Vascular Access Devices (Ports)
Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
Dental Filling Materials, Cushions or Pads made from traditional materials and designs
Denture Repair Kits and Realiners
Digital Mammography [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.]
Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)
Externally Worn Monitors for Insulin Reactions
Functional Electrical Neuromuscular Stimulators
General Biliary Catheters
General Urological Catheters (e.g., Foley and diagnostic catheters)
Jaundice Monitors for Infants
Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
Manual Image Guided Surgery
Menstrual Pads (Cotton or Rayon, only)
Menstrual Tampons (Cotton or Rayon, only)
Nonimplantable Electrical Incontinence Devices
Nonimplantable Male Reproductive Aids with no components that enter the vagina
Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain
Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings)

SIGNIFICANT RISK DEVICES

General Medical Use

Catheters:

- Urology - urologic with anti-infective coatings
- General Hospital - except for conventional long-term percutaneous, implanted, subcutaneous and intravascular
- Neurological - cerebrovascular, occlusion balloon
- Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system
- Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery,
- urological and dental applications
- Surgical Lasers for use in various medical specialties
- Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

Anesthesiology Breathing Gas

Mixers Bronchial Tubes

Electroanesthesia Apparatus

Epidural and Spinal Catheters

Epidural and Spinal Needles

Esophageal Obturators

Gas Machines for anesthesia or analgesia

High Frequency Jet Ventilators greater than 150 BPM

Rebreathing Devices

Respiratory Ventilators

Tracheal Tubes

Cardiovascular

Aortic and Mitral Valvuplasty Catheters

Arterial Embolization Devices Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices

Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices

Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable

Cardiopulmonary Resuscitation (CPR) Devices

Cardiovascular/Intravascular Filters

Coronary Artery Retroperfusion Systems

Coronary Occluders for ductus arteriosus, atrial and septal defects

Coronary and Peripheral Arthrectomy Devices

Extracorporeal Membrane Oxygenators (ECMO)

Implantable Cardioverters/Defibrillators

Laser Coronary and Peripheral Angioplasty Devices

Myoplasty Laser Catheters Organ
Storage/Transport Units Pacing
Leads
Percutaneous Conduction Tissue Ablation Electrodes
Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stents
Replacement Heart Valves
RF Catheter Ablation and Mapping Systems
Ultrasonic Angioplasty Catheters Vascular
and Arterial Graft Prostheses Vascular
Hemostasis Devices

Dental

Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA) Dental
Lasers for hard tissue applications
Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
Subperiosteal Implants
Temporomandibular Joint (TMJ) Prostheses

Ear, Nose, and Throat

Auditory Brainstem Implants
Cochlear Implants
Laryngeal Implants
Total Ossicular Prosthesis Replacements

Gastroenterology and Urology

Anastomosis Devices
Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
Biliary Stents
Components of Water Treatment Systems for Hemodialysis
Dialysis Delivery Systems
Electrical Stimulation Devices for sperm collection
Embolization Devices for general urological use
Extracorporeal Circulation Systems
Extracorporeal Hyperthermia Systems
Extracorporeal Photopheresis Systems
Femoral, Jugular and Subclavian Catheters
Hemodialyzers
Hemofilters
Implantable Electrical Urinary Incontinence Systems
Implantable Penile Prostheses
Injectable Bulking Agents for incontinence
Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
Mechanical/Hydraulic Urinary Incontinence Devices
Penetrating External Penile Rigidity Devices with components that enter the vagina
Peritoneal Dialysis Devices

Peritoneal Shunt Plasmapheresis
Systems Prostatic Hyperthermia
Devices Urethral Occlusion
Devices Urethral Sphincter
Prostheses
Urological Stents (e.g., ureteral, prostatG)

General and Plastic Surgery
Absorbable Adhesion Barrier Devices
Absorbable Hemostatic Agents
Artificial Skin and Interactive Wound and Burn Dressings
Injectable Collagen
Implantable Craniofacial Prostheses
Repeat Access Devices for surgical procedures
Sutures

General Hospital
Implantable Vascular Access Devices (Ports) - if new routes of administration or new design
Infusion Pumps (implantable and closed-loop - depending on the infused drug)

Neurological
Electroconvulsive Therapy (ECT) Devices
Hydrocephalus Shunts
Implanted Intracerebral/Subcortical Stimulators
Implanted Intracranial Pressure Monitors
Implanted Spinal Cord and Nerve Stimulators and Electrodes

Obstetrics and Gynecology
Antepartum Home Monitors for Non-Stress Tests
Antepartum Home Uterine Activity Monitors Catheters
for Chorionic Villus Sampling (CVS) Catheters
Introduced into the Fallopian Tubes Cervical Dilatation
Devices

Contraceptive Devices:

- Cervical Caps
- Condoms (for men) made from new materials (e.g., polyurethane)
- Contraceptive In Vitro Diagnostics (IVDs)
- Diaphragms
- Female Condoms
- Intrauterine Devices (IUDs)
- New Electrosurgical Instruments for Tubal Coagulation
- New Devices for Occlusion of the Vas Deferens
- Sponges
- Tubal Occlusion Devices (Bands or Clips)

Devices to Prevent Post-op Pelvic Adhesions Embryoscopes and
Devices intended for fetal surgery Falloposcopes and
Falloposcopic Delivery Systems Intrapartum Fetal Monitors using
new physiological markers New Devices to Facilitate Assisted
Vaginal Delivery
Thermal Systems for Endometrial Ablation

Ophthalmics

Class III Ophthalmic Lasers

Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in
the eye using new active agents or preservatives with no history of prior ophthalmic/contact
lens use or not generally recognized as safe for ophthalmic use Corneal Implants

Corneal Storage Media

Epikeratophakia Lenticules

Extended Wear Contact Lens

Eye Valve Implants (glaucoma implant)

Intraocular Lenses (IOLs) [21 CFR part 813]

Keratoprotheses Retinal Reattachment Systems: fluids, gases, perfluorocarbons,
perfluoropropane, silicone oil, sulfur hexafluoride, tacks

Viscosurgical Fluids

Orthopedics and Restorative

Bone Growth Stimulators

Calcium Tri-Phosphate Hydroxyapatite

Ceramics Collagen and Bone Morphogenic Protein Meniscus Replacements

Implantable Prostheses (ligament, tendon, hip, knee, finger)

Computer Guided Robotic Surgery

Radiology

Boron Neutron Capture Therapy

Hyperthermia Systems and Applicators

Your comments and suggestions for additional examples are welcome and should be sent to:

Program Operation Staff (HFZ-403)

Office of Device Evaluation

Center for Devices and Radiological Health

Food and Drug Administration

9200 Corporate Blvd.

Rockville, MD 20850

(301) 594-1190

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 1

Policy No. XVIII.

Subject: CONTINUING REVIEW PROCESS

As long as data is being collected for an organized research project, the IRB continues to review the status of the protocol and the details of the continuing data gathering activity. In the initial review, the IRB determines the frequency for re-evaluating the protocol based on the risk assessment provided by the investigator and as determined by the IRB during its review. After the study has begun, the IRB re-evaluates the actual risk/benefit ratio and the appropriate interval for continuing review. Amendments to the protocol or the report of a severe or unexpected adverse event(s) may alter the risk to subjects warranting shorter intervals for continuing review. New knowledge resulting from the research or complaints of unfair treatment by research subjects are also considered by the MLH IRB in the continuing review process and the frequency of review.

If patient accruals have been closed and research interventions are completed but Research Investigators are still collecting follow-up data, the expedited review process may be used.

Rule. The IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less than once every twelve (12) months as required by federal regulations.. Unanticipated risks to subjects or new information that may affect the risk/benefit assessment must be promptly reported to, and reviewed by, the IRB.

A. Procedure for the Research Investigator.

Submit a Continuing Review Form (Form 003) along with the appropriate required documentation which should include copies documenting approval of materials submitted within the last reporting year, the complete protocol, the current informed consent, conflict of interest forms, a list of serious and unexpected adverse events reported during the project period, an annual progress report, and a copy of the current informed consent form and a clean copy of the informed consent form for use in the study for the next approval period.

Part 1, Policy XVIII. CONTINUING REVIEW PROCESS

B. Procedure for the Committee.

The continuing review of a protocol will be assigned to a primary reviewer by the Director of Regulatory Affairs in cooperation with the Chairperson of the MLH IRB. If possible, the primary reviewer will be one of the members who initially reviewed the protocol. If both the original primary reviewers are no longer members of the IRB, the reviewer chosen will be a current board member preferably who is knowledgeable in the area of the research. The primary reviewer and the other members of the IRB will receive the appropriate internal forms, the complete protocol, the current informed consent, a list of serious and unexpected adverse events reported during the project period, and an annual progress report. The primary reviewer will present and discuss the continuing review at a convened meeting of the IRB. The other members of the IRB are expected to be prepared to participate in the continuing review at the convened meeting of the IRB.

The specific procedures to be following during review are as follow:

The primary reviewer discusses the currently active protocol and informed consent and any changes to the protocol and/or informed consent to determine if the information is accurate and complete and if there has been a change in the risk to benefit ratio. Significant new findings are discussed that were or should be provided to the subjects that may affect the subject's willingness to continue participation in the research in accordance with informed consent requirements. Also in the review, the Committee re-evaluates the risk/benefit ratio and the appropriate interval for the next continuing review. The Committee votes to approve, approve with modifications, defer, or disapprove the research materials for a continuing period of no more than twelve months. The decision is determined by a simple majority vote.

C. Procedure for the ORA.

1. The ORA ensures that all active studies are in compliance with their individually assigned interval of review. If the current IRB approval has expired, a written notice is sent to the Research Investigator of this violation of institution policy and procedure and federal regulations. If the Research Investigator is not actively pursuing renewal, a written notice signed by either the Director or Chairperson of the MLH IRB is sent informing the investigator that research activities are suspended as is enrollment of new subjects into the study.
2. Notify the Research Investigator in a letter signed by the Chairperson of the MLH IRB of the action taken by the Board.
3. Maintain records of the foregoing activities.

**POLICY
XVIII REVISED
1/6/2003**

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Part 1

Policy No. XIX.

Subject: FINAL REPORT PROCESS

A. Procedure for the Research Investigator.

1. Research Investigators must immediately notify the ORA, in writing, when the study is being terminated. Forward eighteen (18) copies a completed Final Report (Form 003) to the ORA.
2. Final reports may also, at times, be approved by expedited review following the guidelines outlined in Section V of these procedures (Section V. Expedited Review Process)

B. Procedure for the Committee.

1. If a study has been withdrawn by a sponsor because of a safety reason, the IRB must review the reasons for such withdrawal.
2. Review the final report form for acceptance.
3. Act to approve as is, or to require modification for final approval, or to suspend, or to terminate approval.
4. If subjects are in follow-up, determine the next interval of approval according to the degree of risk to ensure the continued protection of the rights and welfare of research subjects.

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Part 1

Policy No. XX.

Subject: REVISION PROCESS

Revisions are minor changes in previously approved protocols. See

section V. EXPEDITED REVIEW, item A. Revisions.

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Part 1

Policy No. XXI.

Subject: AMENDMENT PROCESS

An amendment or supplement to an original protocol is required when a change is proposed to involve human subjects, or it is proposed to change the involvement of subjects and the involvement is different from that which was initially approved by the IRB.

Further, an amendment of a study in effect is required when changes significantly affect the safety of subjects, or the scope of the investigation, or the scientific quality of the study.

(See 21 CFR

312.30). Examples are: (1) a change in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study; (2) an addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety and (3) an addition of a new investigator to carry out a previously approved protocol except in the case of a treatment IND where a physician is being added.

Rule. Changes to approved research during the period for which approval is given may be initiated without full IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subject; however, the IRB must still be notified of the exception as soon as possible. CFR 46.110(b) and 56.110(b) permit the IRB to use expedited review procedures to review amendments of minimal risk and minor administrative changes to the study protocol.

A. Procedure for the Research Investigator - Promptly submit eighteen (18) copies of the proposed change(s). The submission should include the Protocol Submission Form (Form 001) indicating appropriate information, the protocol if necessary and/or the consent form whichever is affected by the change to the ORA.

- a. Prominently identify amendments to protocol as such, e.g., "Change in Protocol", or to informed consent, e.g., " New Research Investigator" in the report section of Form 001, and
- b. Include a brief description of the change(s) and how the research is affected or include a summary of the modifications as provided by the sponsor.
- c. Changes to the consent form must be highlighted.

Part 1, Policy XXI. AMENDMENT PROCESS

B. Procedure for the Committee.

Amendments to a protocol will be assigned to a primary reviewer by the Director of Regulatory Affairs in cooperation with the Chairperson of the Main Line Hospital IRB. If possible, the primary reviewer will be one of the members who served as the primary reviewer for the original protocol. If both primary reviewers are no longer members or are unavailable, the reviewer chosen will be a current member, one preferably who is knowledgeable in the area of the study. The primary reviewer and the other members will receive the appropriate internal forms, the complete revised protocol, and current and revised informed consent forms, if applicable. The primary reviewers will present and discuss the amendment at a convened IRB meeting. The other members of the IRB are expected to be prepared to participate in the review and discussion of the amendment at the convened meeting of the IRB.

Amendments are processed by the IRB according to the Committee approval criteria and action as described for full Committee review in Section IV.

Rule. The decisions for the Research Investigator may be subject to appeal by Principal Investigators.

Procedure for the Research Investigator

Submit the matter for appeal in letter form to the ORA or request the opportunity to respond in person.

Procedures for the ORA and Chair

Receive all requested appeals of IRB decisions with attached protocols from Principal Investigators and forward those protocols to the Committee for consideration and/or schedule a time and date for the Principal Investigator's personal appearance before the Committee. Consider the Principal Investigator's appeal with the Committee. Send written notification of the Committee's action to the Principal Investigator. Maintain records of appeals.

Procedure for the Committee

Consider the appeal, taking into account all available information.

**POLICY
XXI REVISED
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Part 1

Policy No. XXII.

Subject: **APPEAL PROCESS**

Rule. The decisions of the IRB may be subject to appeal by Research Investigators.

A. Procedure for the Research Investigator. Submit the matter for appeal in letter form to the ORA or request the opportunity to respond in person.

B. Procedure for the ORA and Chair.

1. Receive all requested appeals of IRB decisions with attached protocols from Research Investigators and forward those protocols to the Committee for consideration and/or schedule a time and date for the Research Investigator's personal appearance before the Committee.
2. Consider the Research Investigator's appeal with the Committee. Send written notification of the Committee's action to the Research Investigator.
3. Maintain records of appeals.

C. Procedure for the Committee. Consider the appeal, taking into account all available information.

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Part 1

Policy No. XXIII.

Subject: Unanticipated Problems Involving Risks to Subjects or Others

Purpose

The purpose of this policy is to ensure events that may represent unanticipated problems involving risks to subjects and 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

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.

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

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.

Reportable Problems/Events

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.

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

1. 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.)

2. Information that indicates a change in the 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

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

4. A single occurrence, or more often a small number of occurrences of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
5. Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
6. Change to the protocol without prior IRB review necessary to eliminate an apparent immediate hazard to research subject(s)
7. 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
8. An event for which the protocol requires prompt reporting to the sponsor
9. Complaint of a subject when the complaint indicates unexpected risks or the complaint can not be resolved by the research team
10. Protocol violation (an accidental or unintentional change to the IRB approved protocol) that placed one or more subjects at risk, or has the potential to occur again.
11. An unanticipated adverse device effect. Any serious adverse effect on the health or safety, or any life-threatening problem associated with an investigational device.

Procedures

The PI reports problems under this policy by completing and submitting the MLH IRB Form 004 to the Office of Research Affairs. The report should be submitted as soon as possible after the PI learns of the event but in all cases within 10 working days.

NOTE: When a death is unforeseen and indicates subjects or others are at an increased risk of harm, the PI is required to report the death within 24 hours of knowledge of the event.

The Office of Research Affairs will review the submission to determine if it meets the definition of an unanticipated problem involving risks to subjects or others.

In the rare instance that the ORA Director (or Institutional Official in the absence of the ORA Director) and IRB Chairman (or vice-chairman in the absence of the Chairman) jointly determine that an immediate and life-threatening hazard exists for all subjects enrolling in the study, the Chairman (or vice-chairman) 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 meet the criteria for an unanticipated problem as defined in this policy. All members of the convened IRB receive the report form, the currently approved consent form and any supplemental information deemed relevant by the ORA and the IRB chair to conduct a thorough review. Based on the nature of the event and the

expertise required to assess if the IRB chair or designee acts as the primary reviewer and presents his findings to the convened IRB.

The convened IRB will consider the following actions during its deliberations:

- Accept the report with no additional requirements
- Approve the investigator's proposed changes
- Place the study on administrative hold pending IRB receipt of further information from the PI in a time period not to exceed 60 days
- Modification of the protocol
- Modification of the information disclosed during the consent process
- Providing additional information to past subjects
- Providing additional information to current subjects (This must be done whenever the information relates to the subject's willingness to continue participation)
- Requiring current subjects to re-consent
- Alteration of the frequency of continuing review
- Monitoring of the research and/or consent process
- Requiring additional training of the investigator and/or research team
- Suspension or termination of the research
- Referral to other organizational entities for further investigation

If the IRB determines that the event was an unanticipated problem involving risks to subjects or others, the matter is handled according to SOP XXIV under reporting procedures.

Origination Date: 06-20-2002

Revision Date(s): 12-2-2002

04-2003

05-1-2008

03-2009, Effective Date: 05/01/09

Key Contact: MLH Legal & IRB, Office of Research Affairs

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
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Part 1

Policy No. XXIV.

Subject: UNEXPECTED SERIOUS HARM REPORTING

Rule. Information concerning serious and/or fatal injuries to human subjects must be reported immediately to the IRB.

A. Procedure for the Research Investigator.

1. Report any serious injuries to subjects, regardless of the circumstance or the type of use of a test article, that is, in standard research, emergency use, single patient use, or treatment IND, to the following:
 - (i) by phone or by FAX to the Chair, through the ORA; and
 - (ii) to the appropriate Institution officials, and
 - (iii) to the sponsor. (The sponsor is responsible to telephone the FDA within three [3] days of your notification if the event is an unexpected fatal or life threatening experience).
2. Within five (5) working days of the event, submit to the ORA a description of the event outlined on a Protocol Submission Form (Form 001) a copy of the safety report forwarded to sponsor detailing the adverse reaction(s). Address to the Director of Regulatory Affairs.

B. Procedure for the ORA.

1. Receive appropriate materials outlined above from the Research Investigator and assure sufficiency of the report to determine risk to subjects. Forward to the Committee for review.
2. Send letter signed by the Chairman outlining the action of the Committee to the Research Investigator.

Part 1, Policy XXIV. UNEXPECTED SERIOUS HARM REPORTING

C. Procedure for the ORA for Federally Funded Protocols

1. Receive notice from the Research Investigator and assure sufficiency of the report to determine risk to subjects. Forward to the Committee for review.
2. Report to the OHRP information received by the IRB concerning unanticipated problems involving risks to subjects or others if research conducted or supported by HHS.
3. Report to the FDA, or OHRP, a suspension or termination decision.
4. Send letter signed by the Chair outlining the action of the Committee to the Research Investigator.

C. Procedure for the Committee.

1. Process according to full IRB review procedures as per Section IV.
2. Consider suspension or termination of approval of the research.

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Part 1

Policy No. XXV

Subject: Noncompliance

Policy Purpose

The purpose of this policy is to establish guidelines for handling allegations of non-compliance or instances/findings of non-compliance.

Policy Statement

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 on-going 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 Director of Regulatory Affairs, Chairman of the MLH IRB, Office of Research Affairs, 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) Policy.

Results of audits or review of on-site research records conducted by the Office of Research Affairs 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 the Office of Research Affairs and MLH IRB Chairman, 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 Policy 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 PI and study staff, alone or in consultation with the Office of Research Affairs, the MLH IRB Chairman, 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 can not 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. Incidents/findings of non-compliance are reviewed by Office of Research Affairs and MLH IRB Chairman 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 that the non-compliance is minor in nature, then the process under Section II.D. is followed.

The convened MLH IRB will review reports of non-compliance which have been initially assessed by the Office of Research Affairs and the MLH IRB Chairman to be more than minor in nature. At the convened MLH IRB meeting, the MLH IRB must determine if the non-compliance reported is serious non-compliance, or continuing non-compliance. If it is determined that the 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 Minor

If it is determined by the Office of Research Affairs and the MLH IRB Chairman that the non-compliance was minor and once recognized, the research team took the necessary corrective actions, the Principal Investigator (PI) 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 Office of Research Affairs and the MLH IRB Chairman that the non-compliance was minor but was not recognized and the research team did not take the necessary corrective actions, Office of Research Affairs and/or MLH IRB Chairman will advise the PI and research team of the event and the necessary corrective actions. Alternatively, the Office of Research Affairs and/or MLH IRB Chairman 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 PI and/or the research team;
- Require enrolled subjects to be re-consented or provided 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 PI will be notified in writing and no further action is required under this policy

E. Handling Incidents/Findings of Non-Compliance which are Serious or Continuing

The convened MLH IRB will review reports of non-compliance which are considered by the Office of Research Affairs and the MLH IRB Chairman to be possibly serious or continuing in nature. The PI will be notified in writing that the matter has been sent to the convened IRB for review. The Office of Research Affairs will provide as much information as possible related to incident/finding to all members attending the convened meeting. The information will include at a minimum, the report of incident/finding, the protocol or protocol synopsis, and the informed consent form. The MLH Compliance Office or Office of Research Affairs will present a summary of the events to date to the MLH IRB and propose an initial Plan of Correction to remedy the non-compliance.

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, the Office of Research Affairs 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 participants. Corrective actions may include, but are not limited to, the following:

- Suspend the research;
- Terminate the research;
- Notify current participants 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;
- Require enrolled subjects to be re-consented;
- Modify the continuing review schedule;
- Modify the auditing schedule;
- Monitor the research activities;
- Monitor the consent process.

The determinations of the MLH IRB will be documented in the meeting minutes. The PI and the Institutional Official (IO) will be notified in writing of the determinations of the MLH IRB through the Office of Research Affairs. The written notice will include a request for the PI or investigator to acknowledge, in writing, the receipt of the written notice and agreement to comply with any applicable conditions described therein. The IRB letter 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).

The MLH IRB and IO will report through the Office of Research Affairs 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 the Office of Human Research Protections (OHRP), Food and Drug Administration (FDA), any sponsoring Federal Department or Agency or other sponsoring organization as applicable.

References

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

Replaces

RESPONDING TO ALLEGATIONS OF NON-COMPLIANCE IN A CLINICAL INVESTIGATION,
PART 5, Policy No. V

**PART 1, POLICY XXV
REVISED 10/01/12**

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 1

Policy No. XXVI.

**Subject: SUSPENSION OR TERMINATION OF APPROVAL OF RESEARCH
PROCESS**

Rule. The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or has been associated with unexpected serious harm to subjects.

A. Procedure for the ORA.

1. Promptly forward a letter signed by the Chair of the reasons for the IRB's action to the Research Investigator, the MEC and the OHRP or FDA, if appropriate.
2. Ensure that all research activities are stopped and any subjects currently participating be notified that the study is suspended or terminated. If follow-up of subjects for safety reasons is permitted/required by the IRB, ensure that the subjects are informed and any adverse events/outcomes be reported to the ORA and the sponsor.
3. Maintain information concerning the IRB's reasons for the termination or suspension of IRB approval.

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
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Part 1

Policy No. XXVII.

Subject: SUBMISSION TO HHS PROCESS

The Director of Regulatory Affairs in cooperation with the Chair is responsible for complying with submission requirements to HHS.

A. Procedure for the ORA.

1. Original research

Forward to HHS all exempted research protocols and all protocols approved by the IRB and reported to the MEC which are being submitted for HHS funding. When the IRB approves a protocol on condition that the Research Investigator make modifications to the protocol, the ORA forwards the protocol to HHS only after such modifications are made. As appropriate, the IRB may negotiate protocol modifications with Research Investigators. Each protocol submitted to HHS must include:

- a) certification that the research was reviewed and approved by the IRB established under this Institution's Assurance. The identification numbers of the Assurance and the IRB must be included in the certification; or
- b) certification that the research was reviewed and approved by an IRB established under another assurance. The identification numbers of the approving IRB and the assurance under which it was established along with a copy of the signed cooperative agreement stipulated at Part I, Section II, G (c) of the Assurance must be included with the certification; or
- c) notification that the research was determined to be exempt from coverage under 45 CFR 46. Or that coverage was waived.

Part 1, Policy XXVII. SUBMISSION TO HHS PROCESS

2. Certification Requirements in Cases of Supplements to HHS funded Protocols. a) Submit a

certification to HHS, and when otherwise required by HHS, a supplement to an original protocol, when:

- 1) it is proposed to involve human subjects, and the activity previously had only indefinite plans for the involvement of human subjects; or
 - 2) it is proposed to involve human subjects, and the activity previously had no plans for the involvement of human subjects; or
 - 3) it is proposed to change the involvement of human subjects and that involvement is significantly different from that which was initially approved by the IRB.
- b). Insure that no human subjects are involved in research projects for which the filing of a supplement is required by HHS, prior to review of the submitted supplement and approval by appropriate HHS officials.

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Part 1

Policy No. XXVIII.

Subject: INVESTIGATIONAL NEW DRUG OR DEVICE CERTIFICATION PROCESS

Where HHS sponsors a study that is subject to FDA requirements, the ORA is responsible for complying with the Investigational New Drug or Device Certification Requirement.

A. Procedure for the ORA.

1. Identify the test article (i.e., drug, biologic or device) in the certification to HHS when the proposal involves a test article and state whether the 30-day interval required for test articles has elapsed or was waived by the FDA.
2. If the 30-day interval has expired, state in the certification to HHS whether the FDA has requested that the sponsor continue to withhold or restrict the use of the test article for application in human subjects.
3. If the 30-day interval has not expired and a waiver has not been issued, send a statement to HHS upon expiration of the interval.

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MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 1

Policy No. XXIX

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 research¹ purposes.

Statement of Policy

Protected health information belonging to Main Line Health, Main Line Hospitals, or other MLH Affiliate² 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)*³ means individually identifiable health information.

II. Access to PHI for Research⁴

The use and disclosure of *PHI* for research purposes may be authorized under the following limited circumstances⁵:

¹ 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).

² MLH Affiliate is defined to be an entity of which Main Line Health, Inc. (or a Main Line Health subsidiary) is the parent organization.

³ Complete definitions available at 45 CFR 160.103.

⁴ 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.

⁵ Special rules apply to the use and/or disclosure of psychotherapy notes for research purposes. (Refer to section III. Procedures 8/13/01)

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. Procedures⁶

All requests for *PHI* for research purposes must be made and reviewed in accordance with the procedures explained below.⁷

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. Researchers should be aware that this exception does not permit the continued use or disclosure of the *PHI* once the researcher has determined to go forward with the study.

The MLH IRB may approve the use of *PHI* preparatory to research when the researcher certifies⁸ 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 researcher 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.” Researchers 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*.

Limited information is available to researchers 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 a researcher as part of the work preparatory to developing a research proposal. To access such data, the researcher 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 required. The recipient of the *PHI* must enter into a data use agreement through which the recipient researcher 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

⁶ Any request involving *PHI* may require review by the Chief Privacy Officer for MLH.

⁷ 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](#)

⁸ Certification is 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).

- 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 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 can not 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 unconditioned⁹ components and provide the individual with an opportunity to “opt in”¹⁰ 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.

4. Use/Disclosure with an Approved Waiver of Authorization

The MLH IRB may grant an IRB approved waiver or authorization to allow the use and disclosure of *PHI* (except psychotherapy notes) for research purposes, without subject authorization, when the researcher 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:

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 a researcher 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 Decedents¹¹

⁹ For example, an optional sub-study involving collection of additional blood/tissue samples for banking.

¹⁰ 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.

¹¹ *PHI* of a deceased individual is protected for a period of 50 years following the death of the individual.

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

1. representation that the use or disclosure sought is solely for research on *PHI* of decedents (i.e. researchers 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. representation that 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 MLH Compliance Office: [HIPAA – Patient's Right to Full Accounting of Disclosures Policy](#).

When the records of 50 or fewer individuals are disclosed, the researcher 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 researcher 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 researcher 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: 08/13

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 a all such geographic units containing 20,000 or fewer people is 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 finger prints 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 a researcher 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 researcher 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

OHRP¹² considers private information¹³ 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 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.

¹² 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>

¹³ 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.

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 1

Policy No. XXX

Subject: MAIN LINE HOSPITALS IRB: SURROGATE CONSENT/AUTHORIZATION

Purpose

The purpose of this Policy is to provide Guidelines for the Main Line Hospitals Institutional Review Board (“IRB”) and investigators in proposing, conducting and reviewing research in subjects with decisional impairments.

Policy

It is the policy of the IRB, by and through its sub- committees, 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 procedure will be followed when the researcher determines that a patient is unable to give informed consent for participation in research and/or is unable to give a HIPAA Authorization.

Background

A. Informed Consent

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

Part 1, Policy XXX. Surrogate Consent/Authorization

Pennsylvania law requires the informed consent of the subject or the subject's authorized representative 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 experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment 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 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).)

B. HIPAA Authorization

In addition to obtaining the subject's informed consent, the Health Insurance Portability and Accountability Act ("HIPAA") of 1996 and its implementing regulations require certain entities to obtain a subject's written Authorization for many uses and disclosures of the subject's protected health information ("HIPAA Authorization"). These regulations provide for HIPAA Authorizations to be given by the subject's effective representative under circumstances where the individual is unable to give a HIPAA Authorization.

Procedures

- I. Submission and Review of Protocols Involving Subjects Unable to Provide Informed Consent and/or HIPAA Authorization.**
 - A.** The investigator shall be responsible for making the determination as to whether the research protocol shall or shall not enroll subjects incapable of giving informed consent and/or HIPAA Authorization.
 - B.** If it is anticipated that the research will involve individuals with diminished capacity to consent and/or to give HIPAA Authorization, the protocol shall describe the process by which the investigator will determine and document the individual's ability to provide consent and/or to give HIPAA Authorization. The protocol shall also describe the process by which the investigator shall obtain assent/surrogate consent and/or surrogate HIPAA Authorization.

Part 1, Policy XXX. Surrogate Consent/Authorization

- C.** The IRB shall review such protocols and determine and document whether:
1. the risks to the subjects are reasonable in relationship to any anticipated benefits to subjects and to the importance of the knowledge that may reasonably be expected to result,
 2. the description of the informed consent process to be used is appropriate to the risk of the protocol as assigned by the IRB,
 3. the appropriateness of the assent/surrogate consent process described in the protocol for obtaining informed consent/authorization,
 4. the appropriateness and effectiveness of the HIPAA Authorization if included as part of the informed consent or assent, and
 5. 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 insure that the rights of such subjects are protected. Such additional protections that the IRB may consider may include, but are not limited to:
1. Witnessing of assent/informed surrogate consent and/or surrogate HIPAA Authorization by a third party.
 2. Independent advocate assessment of subjects' ability to assent, and/or surrogates ability to consent and/or provide HIPAA authorization (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.
 3. The appropriateness of the individual serving as the personal representative/surrogate for purposes of the HIPAA Authorization.
 4. Other safeguards as appropriate.
- E.** The IRB shall not approve any research involving the use of surrogate consent and/or surrogate HIPAA Authorization 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 Subjects Ability to Provide Informed Consent and/or HIPAA Authorization in a Research Study

- A.** The investigator shall be responsible for determining whether an individual subject can provide informed consent and/or HIPAA Authorization.
- B.** The investigator will document in the research record, as thoroughly as possible, the reason for the subject's inability to provide informed consent and/or HIPAA Authorization.
- C.** The investigator shall apply and document any additional safeguards as directed by the IRB.

Part 1, Policy XXX. Surrogate Consent/Authorization

III. Individuals Able to Provide Effective Surrogate Consent and/or Surrogate HIPAA Authorization.

For Adults and emancipated minors. The following individuals may be considered legally authorized representatives of the subject and capable of providing surrogate consent and/or surrogate HIPAA Authorization:

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 proxy 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;
 - b. Natural or adoptive parent;
 - c. Adult child;
 - d. Adult brother or sister;
 - e. An adult individual with significant personal relationship with the subject to warrant their authority. (In situations as described in this subsection e, Investigator should document the reasons why such relationship is considered to be significant.)

IV. Responsibilities of the Authorized Individual in the Surrogate Consent Process

The surrogate should base his or her decision on the subject's expressed wishes 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 patient 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.

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 and/or HIPAA Authorization, the investigator shall obtain the legally effective informed consent and/or HIPAA Authorization of the subject for continued participation in the research and for the continued use and/or disclosure of their protected health information as provided for in the original HIPAA Authorization.

Part 1, Policy XXX. Surrogate Consent/Authorization

- B.** Decision-making capacity of subjects may fluctuate. The consent process should be ongoing and involve the legally effective representative if at any time the investigator believes that the subject is unable to provide informed consent for continuing in a research project in which the subject initially gave informed consent and HIPAA Authorization. No re-consent of HIPAA Authorization is required if the subject was capable of giving valid HIPAA Authorization at the onset of the research.

VI. Cross Reference and Application of the term “Surrogate” as defined in this Policy.

For references in IRB Policies and Procedures to “legally authorized representative” or “subject’s representative,” this **IRB: Surrogate Consent/Authorization Policy** applies.

Origination Date: 12-02-04

Revision

Date: Review

Date:

Previous Revision Date:

Key Contact: MLH Legal & IRB Office of Research Affairs

Cross Reference: Main Line Hospitals IRB Policy and Procedure Manual

PART 2

SPECIAL PROCEDURES FOR VULNERABLE SUBJECTS

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 2

Policy No. I

Subject: Research Activities Involving Pregnant Women, Fetuses and Human in Vitro Fertilization (45 CFR 46 Subpart B)

Rule. Only research which satisfies the conditions of all applicable sections of Subpart B of Title 45 CFR 46 shall be approved by the IRB. (Copy of 45 CFR 46 is in the IRB Office). No such activity may be undertaken unless:

- Appropriate studies on animals and non-pregnant individuals have been completed;
- Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.
- Individuals engaged in the activity will have no part in:
 - any decisions as to the timing, method, and procedures used to terminate the pregnancy, and
 - determining the viability of the fetus at the termination of the pregnancy; and
- No procedural changes which may cause greater than minimal risk to the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.
- No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

A. Pregnant Women. "Pregnancy" encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus.

1. IRB duties.

- a. Assess the purpose of the research, whether it is directed toward the mother's health or toward the fetus.
- b. Determine permissibility of the research, that no pregnant woman is involved as a subject unless either:
 - 1) the purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or

- 2) the risk to the fetus is minimal.
- c. Determine appropriateness of the research, that all aspects of the activity meet the requirements of the rule as set forth above.
- d. Assess the degree of risk/benefit of the research, 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.
- e. Evaluate inclusion criteria, that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision will be made by the IRB for monitoring the actual informed consent process.
- f. Examine informed consent process, that research activity only be conducted if the pregnant woman and the father of the fetus are legally competent and have given their informed consent after having been fully informed of possible impact on the fetus, except that the father's consent need not be secured if:
 - 1) his identity or whereabouts cannot reasonably be ascertained,
 - 2) he is not reasonably available, or
 - 3) the pregnancy resulted from rape.

2. Investigator responsibilities.

- a. Provide for the inclusion/exclusion of pregnant women in the proposed research according to the foregoing rule and IRB determinations. See 45 CFR 46.207.
- b. Submit certification to DHHS that the IRB has made the determinations required under 45 CFR 46.205(a) if applicable.
- c. Obtain informed consent from the pregnant woman and the father of the fetus (if appropriate) as set forth above.

B. Live Fetuses in utero. "Fetus" means the product of conception from the time of implantation (as evidenced by any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until a determination is made, following expulsion or extraction of the fetus, that it is viable.

1. IRB duties.

- a. Determine permissibility of the research,
 - 1) that the purpose of the research is to meet the health needs of the particular fetus thus benefiting the fetus directly, or to meet the health needs of the mother thus benefiting the fetus indirectly, or to meet the health needs of both in which latter two cases, the regulations pertaining to pregnant women also apply, or
 - 2) that the risk to the fetus imposed by the research is minimal and purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means.
- b. Assess the degree of risk /benefit of proposals for research on fetal therapy, that the risks are justified by a reasonable possibility of benefiting the fetus,

- c. Examine the informed consent process, that research activity only be conducted if the pregnant woman and the father of the fetus are legally competent and have given their informed consent after having been fully informed of possible impact on the fetus, except that the father's consent need not be secured if:
 - 1) his identity or whereabouts cannot reasonably be ascertained,
 - 2) he is not reasonably available, or
 - 3) the pregnancy resulted from rape.

2. Investigator responsibilities.

- a. Provide for the inclusion/exclusion of live fetuses in utero in the proposed research according to the foregoing rule and IRB determinations. See 45 CFR 46.208.
- b. Obtain informed consent from mother and father (if appropriate) according to the above.

C. Fetuses ex utero, including nonviable fetuses as subjects.

1. A "viable ex utero fetus" means a fetus likely to survive to the point of sustaining life independently, given the benefit of available medical therapy; it is then called an "infant" and comes under the regulations dealing with children
2. A "nonviable ex utero fetus" means a fetus which, although living, is not viable. That is, it cannot possibly survive to the point of sustaining life independently, even with the support of available medical therapy, and will therefore die. Research involving a nonviable fetus that would either artificially maintain vital functions or hasten their failure is forbidden.

1. IRB consideration.

- a. Until it has been ascertained whether or not a fetus ex utero is viable, a fetus ex utero may not be involved as a subject in an activity unless:
 - 1) there will be no added risk to the fetus resulting from the research activity, and the purpose if the activity is the development of important biomedical knowledge that cannot be obtained by other means,
 - 2) the purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.
- b. No nonviable fetus may be involved as a subject in a research activity unless:
 - 1) vital function of the fetus will not be artificially maintained,
 - 2) experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and
 - 3) the purpose of the activity is the development of important biomedical knowledge that cannot be obtained by other means.
- c. In the event the fetus ex utero is found to be viable, it is then called an infant and may be included as a subject in the activity according to the Procedures dealing with children. See Section III.

2. IRB Duties.

- a. Determine the status of fetus ex utero as a proposed research subject, whether viable or non-viable.
- b. Determine that the purpose of the research is
 - 1) to develop important biomedical knowledge that cannot be obtained by other means and there will be no added risk to the fetus as a result of the activity.
 - 2) to enhance the possibility of survival of the particular fetus to the point of viability.
- c. Determine when the research includes only viable fetuses ex utero that they may be included as subjects in the activity only to the extent permitted by and in accordance with the requirements set forth for children involved as subjects in research. See 45 CFR 46.209(c)
- d. Determine when the research includes nonviable fetuses ex utero that they may be involved as subjects only according to the aforementioned limitations. See 45 CFR 46.209 (d)
- e. Examine the informed consent process, that research activity only be conducted if the mother and the father of the fetus are legally competent, and have given their informed consent after having been fully informed of possible impact on the fetus except that the father's consent need not be secured if:
 - 1) his identity or whereabouts cannot reasonably be ascertained,
 - 2) he is not reasonably available, or
 - 3) the pregnancy resulted from rape.

3. Investigator responsibilities.

1. Provide for the inclusion/exclusion of nonviable/viable fetuses ex utero in the proposed research in accordance with the aforementioned considerations and limitations.
2. Obtain informed consent from mother and father (if appropriate) according to Section C.2.e.

(Proposed changes concerning father's consent have been published.)

D. In vitro fertilization. This type of research is not permitted at Main Line Hospitals, Inc.

In vitro fertilization. "In vitro fertilization" means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

1. IRB Duties

- a. In addition to the responsibilities prescribed for IRBs under 45 CFR 46 Subpart A, the IRB will carry out the following additional duties

- 1) determine that all aspects of the activity meet the requirements of 45 CFR

46 Subpart B.

- 2) determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made by the applicant or officer for monitoring the actual informed consent process by (i) overseeing the actual process by which individual consents required by Subpart B are secured either by approving induction of each individual into the activity or verifying that approved procedures for induction of individuals into the activity are being followed and (ii) monitoring the progress of the activity and intervening as necessary to determine if any unanticipated risks have arisen.

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Part 2

Policy No. II

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

Rule: The involvement of prison inmates in research was once common because the stability of prison life (e.g. controlled diet, ready availability of subjects for followup) made prisons attractive research environments. More recently, however, ethicists and others concerned with the treatment of human participants in research recognized that the very fact of incarceration may make it difficult or impossible for prisoners to give voluntary, informed consent. In response to this growing concern, the **National Commission for the Protection of Human Subjects** was asked to consider the problem; the Commission issued its report and recommendations in 1976. In 1978, DHHS issued specific regulations governing research with prisoners [45 CFR 46 Subpart C]. The implementation of FDA regulations on research involving prisoners has been stayed until further notice [21 CFR 50 Subpart C]. Some federal agencies significantly limit the involvement of prisoners in biomedical research (e.g., Federal Bureau of Prisons).

A. Composition of the IRB

In addition to satisfying the requirements in Sec. 46.107, an Institutional Review Board shall meet the following specific requirements:

1. A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.
2. At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

B. IRB Duties

1. In addition to all other responsibilities prescribed for the Main Line Hospitals Institutional Review Board under 45 CFR 46, the Board shall review research

- covered by Subpart C and approve such research only if it finds that:
- a The research under review represents one of the categories of research permissible under Sec. 46.3069(a)(2);
 - b Any possible advantages accruing to the prisoner through his/her participation in the research, when compared to the general living conditions, medical care, 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;
 - c The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;
 - d 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 Board 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 particular research project.
 - e The information is presented in language which is understandable to the subject population;
 - f 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; and
 - g Where the Board finds there may be a need for follow-up examination or care of participants 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 participants of this fact.
2. Biomedical or behavioral research conducted or supported by DHHS may involve prisoners as subjects only if:
- a The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under Sec. 46.305 of Subpart C; and
 - b. In the judgment of the Secretary the proposed research involves solely the following:
 - i 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;
 - ii Study of 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;
 - iii Research on 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
- iv Research on 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 his intent to approve such research.
- c. Except as provided in paragraph (a) of this section, biomedical or behavioral research conducted or supported by DHHS shall not involve prisoners as subjects.

NOTE: THIS GUIDANCE REPLACES THE FOLLOWING OHRP GUIDANCE: "OHRP Guidance on Approving Research Involving Prisoners " (May 19, 2000) [CLICK HERE](#)
THIS GUIDANCE HAS BEEN UPDATED FOR FORMAT AND TO PROVIDE ADDITIONAL GUIDANCE ON RESPONSIBILITIES OF IRBs AND INSTITUTIONS REQUIRED UNDER SUBPART C

**Office of Human Research Protections
Department of Health and Human Services**

OHRP Guidance on the Involvement of Prisoners in Research

Date: May 23, 2003

Scope: This document describes the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR part 46, subpart C, which provides additional protections to prisoners involved as subjects in HHS-conducted or supported research.

Target Audience: Research institutions, institutional review boards (IRBs), investigators, and sponsors.

For further information contact: OHRP Prisoner Research Contact Person at (301) 496-7005 (phone); (301) 402-0527(fax)

A. General Regulatory Background

HHS regulations at 45 CFR part 46, subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners as subjects. The regulations are applicable to all biomedical and behavioral research conducted or supported by HHS. See 45 CFR 46.301. It is important to note that the regulations provide that "biomedical or behavioral research conducted or supported by HHS shall not involve prisoners as subjects" unless the research is specifically authorized within the subpart. See 45 CFR 46.306(b).

In the preamble to the final subpart C rule, the drafters noted: "In fact, most testimony before the Commission opposed the use of prisoners in any form of medical research not intended to benefit the individual prisoner." 43 Fed. Reg. 53652,53653 (November 16, 1978). HHS did determine that some limited research would be permissible but not "until additional and more stringent review procedures are conducted." Id. at page 53652.

B. Subpart C applies where any subject is or becomes a prisoner.

The provisions of subpart C apply to any research conducted or supported by HHS in which prisoners are subjects. This includes situations where a human subject becomes a prisoner after the research has commenced. As the Purpose section of the regulation notes: "Inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and

uncoerced decision whether or not to participate as subjects in research, it is the purpose of this subpart to provide additional safeguards for the protection of prisoners involved in activities to which this subpart is applicable." 45 CFR 46.302. These concerns apply whether the research involves individuals who are prisoners at the time of enrollment in the research or who become prisoners after they become enrolled in the research. In the latter situation, it is unlikely that review of the research and the consent document contemplated the constraints imposed by incarceration.

C. What does the definition of prisoner encompass?

"Prisoner" is defined by HHS regulations at 45 CFR part 46.303(c) as "any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a 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."

D. Special Composition of IRB

In addition to satisfying the requirements of 45 CFR 46.116 and 46.117, when an IRB reviews a protocol involving prisoners as subjects that is conducted or supported by HHS, the composition of the IRB must satisfy the following requirements of HHS regulations at 45 CFR 46.304(a) and (b):

- A majority of the IRB (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the IRB.
- At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

In the absence of choosing someone who is a prisoner or has been a prisoner, the IRB should choose a prisoner representative who has a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner.

In addition, the IRB must notify OHRP of any change in the IRB roster occasioned by the addition of a prisoner or a prisoner representative, as required by HHS regulations at 45 CFR 46.103(b)(3). IRBs should be alert to the impact of roster changes on quorum requirements under HHS regulations at 45 CFR 46.108(b).

If a protocol involving prisoners as subjects is to be reviewed by more than one IRB, only one IRB must satisfy the requirement that at least one member of the IRB be a prisoner or a prisoner representative.

For research involving prisoners as subjects, the IRB must meet the special composition requirements of 45 CFR 46.304 for all types of review of the protocol, including initial review, continuing review, review of protocol amendments, and review of reports of unanticipated problems involving risks to subjects.

E. Additional duties of the IRB where prisoners are involved.

When an IRB is reviewing a protocol in which a prisoner is a subject, the IRB must make, in addition to other requirements under 45 CFR 46, subpart A, seven additional findings under 45

CFR 46.305(a), as follows:

- (1) the research under review represents one of the categories of research permissible under 45 CFR 46.306(a)(2);
- (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, quality of food, amenities and opportunity for earnings in the prison, are not of such a 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 nonprisoner 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 particular research project;
- (5) the information is presented in 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; and
- (7) where the IRB finds there may be a need for follow-up examination or care of participants 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 participants of this fact.

F. Permitted research involving prisoners.

For research conducted or supported by HHS to involve prisoners, two actions must

occur: (1) the institution engaged in the research must certify to the

Secretary

(through OHRP) that the IRB designated under its assurance of compliance has reviewed and approved the research under 45 CFR 46.305; and

(2) the Secretary (through OHRP) must determine that the proposed research falls within the categories of research permissible under 45 CFR 46.306(a)(2). The categories of permissible research are the following:

(i) 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;

(Note that the definition of minimal risk for prisoner research at 45 CFR 46.303(d) differs from the definition of minimal risk for other research, contained in 45 CFR 46, subpart A, 45 CFR 46.102(i))

[See Section J.7 of this document]

(ii) study of 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;

(iii) research on 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 (through OHRP) 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

(iv) research on 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 (through

OHRP) 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.

G. Responsibilities of IRBs: Documentation of IRB Findings Required Under Subpart C

Pursuant to HHS regulations at 45 CFR 46.115(a), an institution or, when appropriate, an IRB, shall prepare and maintain adequate documentation of IRB activities. For the purposes of subpart C, the IRB activities include making the specific findings required under HHS regulations at 45 CFR 46.305(a). OHRP would consider documentation of protocol-specific information justifying each IRB finding required under 45 CFR 46.305(a) to be one way of adequately documenting the IRB activities required under subpart C.

H. Responsibilities of Institutions

Pursuant to HHS regulations at 45 CFR 46.115(a), an institution must maintain adequate documentation of IRB activities. These records must be made accessible to authorized representatives of HHS, at reasonable times and in a reasonable manner, under HHS regulations at 45 CFR 46.115(b). OHRP recommends that one way for an institution responsible for the conduct of the proposed research to adequately document the IRB review of the research:

- The curriculum vitae of the prisoner or prisoner representative serving on the IRB.
- A record of the determination of the IRB regarding the seven additional findings required under HHS regulations at 45 CFR 46.305(a).

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is supported by HHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a). The institution must send to OHRP a certification letter to this effect, which should also include the name and address of the institution and specifically identify the research protocol in question and any relevant HHS

grant application or protocol. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to the institution on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP a copy of the research proposal so that OHRP can determine whether the proposed research involves one of the categories of research permissible under 45 CFR 46.306(a)(2), and if so, which one. The term "research proposal" includes the IRB-approved

protocol, any relevant HHS grant application or proposal, any IRB application forms required by the IRB, and any other information requested or required by the IRB to be considered during initial IRB review.

Prisoner research certification letters should be mailed to:

Attention: OHRP Prisoner Research Contact Person
Office for Human Research Protections
Department of Health and Human
Services The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

I. Responsibilities of OHRP

Following receipt of the research proposal, OHRP will determine which, if any, of the four categories of research permissible under HHS regulations at 45 CFR 306(a)(2) the proposed research meets. OHRP will consult with appropriate experts with respect to certain research that falls under paragraphs (iii) and (iv) of 45 CFR 46.306(a)(2).

When applicable, OHRP also will publish in the Federal Register a notice of intent to approve such research. HHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its approval in writing to the institution on behalf of the Secretary under 45 CFR 46.306(a)(2).

J. Frequently Asked Questions

1. Does subpart C apply only where the research targets prisoners as subjects?

Answer: No, subpart C applies whenever any human subject in a research protocol subject to 45 CFR part 46 becomes a prisoner at any time during the study.

2. What should an investigator do if a subject becomes a prisoner after enrollment in research?

Answer: The investigator should report this situation to the IRB immediately.

3. What should be done when a subject becomes a prisoner after enrollment in a study which was not reviewed and approved by the IRB in accordance with the requirements of subpart C?

Answer: When a previously enrolled research subject becomes a prisoner and the relevant research protocol was NOT reviewed and approved by the institutional review board (IRB) in accordance with the requirements of HHS regulations at 45 CFR part 46, subpart C, the principal investigator should promptly notify the IRB of this event. All research interactions

and interventions with, and obtaining identifiable private information about, the now- incarcerated prisoner-subject must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.

NOTE: OHRP has allowed one important exception. In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

Upon receipt of notification that a previously enrolled research subject has become a prisoner, the IRB should promptly re-review the protocol in accordance with the requirements of subpart C if the principal investigator wishes to have the prisoner subject continue to participate in the research.

It is important that the IRB remind the principal investigator that, except in the special circumstances noted above, all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-subject must cease until all of the requirements of subpart C have been satisfied with respect to the relevant protocol.

4. Is an adolescent (e.g., age 14) detained in a juvenile detention facility a prisoner?

Answer: Yes. In addition to subpart C, most likely subpart D would also apply.

5. Can research involving prisoners be expedited?

Answer: Yes, however, OHRP recommends that the convened IRB review research involving prisoners as human subjects.

6. Do the exemptions apply to research involving prisoners?

Answer: The exemptions at 45 CFR 46.101(b) do not apply to research involving prisoners. See 45 CFR 46.101(i), footnote 1.

7. What is the definition of minimal risk for prisoner research?

Answer: The definition of minimal risk for research involving prisoners can be found at 45 CFR 46.303(d). This definition, promulgated in 1978, differs from the definition of minimal risk in subpart A of 45 CFR 46. See 45 CFR 46. 102(i).

For research involving prisoners, the definition of minimal risk requires reference to physical or psychological harm, as opposed to harm or discomfort, to risks normally encountered in the daily lives, or routine medical, dental or psychological examination of healthy persons.

<p>Definition of Minimal Risk in Prisoner Research 45 CFR 46.303(d)</p>	<p>Definition of Minimal Risk in 45 CFR part 46, subpart A, 45 CFR 46.102(i)</p>
<p>"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.</p>	<p>"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.</p>

Last revised: June 25, 2004

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Part 2

Policy No. III

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

Rule. Only research which satisfies the conditions of all applicable sections of Subpart D (above) and the NIH policy on the Inclusion of Children in Research where the research is supported or conducted by the NIH may be approved by the IRB. Generally, healthy children can be studied when the research is considered as "not greater than minimal risk". Children can be involved in research with greater than minimal risk only when it presents the prospect of direct benefit to the individual child or is likely to yield generalizable knowledge about the child's disorder or condition. [On March 6, 1998 the NIH issued Policy and Guidelines on the Inclusion of Children as participants in Research Involving Human Subjects effective after October 1, 1998. The NIH policy requires that children (defined by the NIH as individuals under the age of 21) be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. The policy was developed because medical treatments applied to children are often based upon testing done only in adults, and scientifically evaluated treatments are less available to children due to barriers to inclusion in research studies. A copy of the NIH Policy is available in the IRB Office.]

Children defined.

Children are persons who have not attained the age of 18 or have other status which allows them to effectively consent to treatments or procedures involved in the research. In the Commonwealth of Pennsylvania a person 18 years of age or older, or who had graduated from high school, or has married, or has been pregnant may give effective consent to medical, dental and health services. [35PaSA Section 10103] The NIH policy defines children as being under 21. The FDA definition of a child is an individual from infancy to 16 years of age. Generally, State laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, State laws vary, and many do not address when a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on State definitions of "child" for consent purposes.

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.

A. 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.

2. Assent/waiver. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, 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.
3. 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 - see 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.

B. 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.
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 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. Assent must 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 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.

C. Assent Documentation

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 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/Co-investigator signature

Date

Part 2, Policy III. RESEARCH ACTIVITIES INVOLVING CHILDREN AS
SUBJECTS (45 CFR 46 Subpart D)

D. IRB duties.

1. Determine permissibility of the research, that the purpose of research activities involving children is appropriate to their age and represents one of the following four permissible categories of research:
 - a. Research not involving greater than minimal risk, only if the IRB finds that: Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. (See Section A.3.)
 - b. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual subject, only if the IRB finds that:
 - 1) the risk is justified by the anticipated benefit to the subjects;
 - 2) the relation of the anticipated benefit to risk is at least as favorable to the subjects as that presented by available alternative approaches; and
 - 3) adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians. (See Section A.3.)
 - c. 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, only if the IRB finds that:
 - 1) the risk represents a minor increase over minimal risk;
 - 2) 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;
 - 3) 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
 - 4) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians. (See Section A.3.)
 - d. 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, only if the IRB finds that:
 - 1) 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
 - 2) the Secretary, 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.
 - 3) adequate provisions are made for soliciting assent of the children and permission of their parents or guardians. (See Section A.3.)

Part 2, Policy III. RESEARCH ACTIVITIES INVOLVING CHILDREN AS
SUBJECTS (45 CFR 46 Subpart D)

2. 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.
3. Require compliance with the "NIH Policy on The Inclusion of Children as Participants in Research Involving Human Subjects" if the study is an NIH application/proposal or NIH intramural project.
 - a. It is the policy of NIH that when there is sound scientific rationale for including children in research involving adult human subjects, children (i.e., individuals under the age of 21 as defined by the NIH) must be included, unless there are scientific and ethical reasons not to include them.
 - b. Application proposals for research involving human subjects must include a section titled, "Participation of Children" which should provide either a description of plans to include children or a rationale for excluding them.
 - 1) inclusion plans must justify the age range to be used, describe the expertise of the research team with regard to children at the age ranges included, describe appropriateness of the facilities to accommodate the children, and indicate the number of children to be included sufficient to contribute to a meaningful analysis relative to the aim of the research.
 - 2) exclusion plans must present acceptable justification.
4. 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.
5. 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.
6. Examine informed consent document and process.

Part 2, Policy III. RESEARCH ACTIVITIES INVOLVING CHILDREN AS
SUBJECTS (45 CFR 46 Subpart D)

E. Investigator responsibilities.

1. Provide for inclusion/exclusion of children in the proposed research according to 45 CFR 46 Subpart D, the IRB determination and the NIH Policy, if applicable.
2. Solicit assent from the children as required by the IRB and permission of their parents or guardians as set forth herein.

Office for Human Research Protections (OHRP) Special Protections for Children as Research Subjects Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process

Date: May 26, 2005

Scope:

This document provides guidance on the HHS 45 CFR 46.407 review process ("407 review process") as required under subpart D of HHS Protection of Human Subjects Regulations at 45 CFR part 46. In particular, the Office for Human Research Protections (OHRP) offers guidance on the following topics:

- (1) IRB findings necessary to submit a protocol to OHRP for 407 consideration and/or review;
- (2) steps in the submission process;
- (3) OHRP's response to submissions;
- (4) the schedule and details for 407 panel review; and
- (5) potential outcomes of the 407 review process.

This guidance applies to HHS- conducted or -supported research.

NOTE: Protocols meeting the conditions of 45 CFR 46.407 also may be subject to Food and Drug Administration (FDA) regulations under 21 CFR 50.54 if the protocols involve a clinical investigation of an FDA-regulated product. Other protocols may be subject to FDA regulation at 21 CFR 50.54 but not subject to HHS regulations at 45 CFR 46.407. Although this guidance document briefly addresses steps that would be taken when FDA regulations apply, it is focused on the 407 review process for research solely within OHRP's purview. The reader is advised to consult with FDA in the event that the review process falls within FDA's regulatory purview. [FDA Contact Information: Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration, 5600 Fishers Lane, Room 48-44, HFG-2, Rockville, MD 20857, (301) 827-1996.]

Target Audience: Institutions, Institutional Review Boards (IRBs), investigators, and HHS funding agencies.

General Regulatory Background:

HHS regulations at 45 CFR part 46 include subpart D, Additional Protections for Children Involved as Subjects in Research. All studies involving children, conducted or supported by HHS, which are not otherwise exempt, require IRB review in accordance with the provisions of subpart D. If an institution's IRB does not believe the proposed research meets the requirements of 45 CFR 46.404, 46.405, or 46.406 of subpart D (described below), but finds and documents that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children (in accordance with HHS regulations at 45 CFR 46.407(a)), the IRB or other appropriate institutional official may submit the protocol and supporting materials to OHRP for HHS consideration under the provisions of 45 CFR 46.407(b). Before submitting a protocol to OHRP, the IRB must determine that, in addition to meeting the requirements of 45 CFR

46.407(a) and other applicable sections of subpart D, the proposed research also meets all of the requirements of 45 CFR part 46, subpart A.

HHS will consult with a panel of experts under 46.407 only when the proposed research is conducted or supported by HHS. Note that if an institution has elected in its assurance to apply all of the subparts of 45 CFR part 46 to all of its human subjects research regardless of the source of support, and the IRB finds that the proposed research meets the conditions for review under 46.407, the IRB is not required to submit the protocol to OHRP for review if the research under consideration is not supported by HHS. In such cases, OHRP recommends that the institution consult with appropriate officials at the relevant federal agency or department supporting the research. When such research is supported by a non-federal sponsor, OHRP recommends that the institution consider convening an independent panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and provide an opportunity for review and comment by the local community where the research is to be conducted before deciding whether to proceed with the research.

Subpart D permits IRBs to approve three categories of research involving children as research subjects:

45 CFR 46.404 - Research not involving greater than minimal risk to the children. To approve this category of research, the IRB must make the following determinations:

- the research presents no greater than minimal risk to the children; **and**
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research. To approve research in this category, the IRB must make the following determinations:

- the risk is justified by the anticipated benefits to the subjects;
- the relation of the anticipated benefit to the risk presented by the study is at least as favorable to the subjects as that provided by available alternative approaches; **and**
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

45 CFR 46.406 - Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition. In order to approve research in this category, the IRB must make the following determinations:

- the risk of the research represents a minor increase over minimal risk;
- the intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations;

- 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 disorder or condition; **and**
- adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

A fourth category of research requires a special level of HHS review beyond that provided by the IRB.

45 CFR 46.407 B Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

If the IRB believes that the research does not meet the requirements of 45 CFR 46.404, 46.405, or 46.406, but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, it may refer the protocol to HHS for review. The research may proceed only if the Secretary, HHS, or his or her designee, after consulting with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following an opportunity for public review and comment, determines either: (1) that the research in fact satisfies the conditions of 45 CFR 46.404, 46.405, or 46.406, or (2) the following:

- the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- the research will be conducted in accordance with sound ethical principles; **and**
- adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

If the research involves a product that is FDA-regulated, FDA's regulatory requirements at 21 CFR 50.54 must also be met.

Guidance:

What Findings Should IRBs Make before Submitting a Protocol to HHS for 407 Consideration and/or Review?

The IRB must determine that the protocol does not meet the conditions for approval of research under HHS regulations at 45 CFR 46.404, 46.405, or 46.406 as described above.

Before submitting a request to OHRP for a review under the 407 process, the IRB also must determine that the proposed research and the parental permission/assent forms comply with all regulatory requirements and are otherwise approvable (i.e., meet the regulatory requirements under 45 CFR 46.111, 46.408, and 46.409), with the exception of the need for review under the 407 process. Any modifications to the protocol or parental permission/assent forms required by the IRB to comply with 45

CFR 46.111, 46.408, or 46.409 must be made by the principal investigator before materials are submitted to OHRP for consideration.

What are the Steps in the Referral Process?

1. IRB Request for 407 Review

Once an IRB determines that a protocol does not meet the requirements of 46.404, 46.405, or 46.406 for approval of research, but does meet the requirements for review under 45 CFR 46.407(a), the institution or the IRB may request that OHRP, on behalf of the Secretary, HHS, conduct a 46.407 review. In order for OHRP to determine whether a 407 review should proceed, the institution must submit the following documents/information to OHRP in both written and electronic (if available) forms:

- a. IRB documentation of required findings under 45 CFR 46.407C that the proposed research does not meet the requirements of 46.404, 46.405, or 46.406 but presents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
- b. Institution name, institution assurance number, and IRB name.
- c. Institutional contact's name, title, phone number, fax number, mailing address, and email address.
- d. Title of protocol, and name of principal investigator(s).
- e. HHS application number and name of funding agency.
- f. Relevant HHS grant application or proposal.
- g. Most current version of protocol and grant application submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
- h. Most current version of parental permission/assent documents submitted to and reviewed by the IRB and modified by the principal investigator if required by the IRB.
- i. Relevant IRB minutes and correspondence.

Hard copy versions of the materials should be sent to:

Division of Policy and Assurances
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

OHRP will provide the submitting institution with instructions for transmitting documents electronically.

OHRP will notify the relevant HHS funding agency that it has received a request for a 407 review of a protocol. OHRP will request information from the agency about the outcome of the merit review of the research (i.e., the summary statement of the relevant Scientific Review Group or the evaluation of the proposal).

2. OHRP's Initial Evaluation of the Request for 407 Review

After receiving the materials listed above, OHRP will review the protocol and supporting information to evaluate whether the conditions for review under 46.407 by an expert panel have been met. In the process of this review OHRP may request additional information or clarification from the IRB. In all cases, OHRP will confer with FDA to determine if FDA regulations under 21 CFR 50.54 also apply. In cases where FDA regulations do apply, OHRP has delegated its authority to FDA to convene a panel of experts to both review the research and to advise the Secretary (see discussion at the end of this guidance). In all cases, OHRP will notify the IRB, the investigator, and the funding agency in writing of its evaluation, which generally would include one of the following outcomes:

- a. the information submitted to OHRP is insufficient to enable OHRP to evaluate whether a review of the proposed research under HHS regulations under 45 CFR 46.407 is appropriate; **or**
- b. the research might be approvable under 46.404, 46.405, or 46.406, and the IRB should reconsider its evaluation of the protocol; **or**
- c. the research fulfills the criteria for consideration by HHS under the provisions of 46.407 and OHRP will initiate the review process; **or**
- d. the research fulfills the criteria for consideration by HHS under the provisions of 46.407, and because FDA regulations also apply, FDA will convene a panel of experts in coordination with OHRP to review the protocol.

When OHRP has sole responsibility for the 407 review process (i.e., FDA regulations do not apply), the schedule described below is initiated.

3. OHRP Schedule for 407 Review Process When FDA Regulations Do Not Apply

If OHRP has determined that the conditions for 407 review have been met and that FDA regulations do not apply, OHRP will identify a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and relevant child advocates to review the protocol. Potential experts will undergo an initial screening for conflicts of interest. Potential experts will be informed that they will be asked to provide individual written recommendations and that their reports, as well as their identities, will be publicly available during the public review and comment period.

As noted above, OHRP will notify the funding agency that a referral for a 407 review has been received and accepted. If the research is a multi-site protocol, the funding agency may consider the implications of the 407 review process on the conduct of the research at the other sites and would have the option of delaying or suspending subject enrollment at these other sites pending the outcome of the 407 review. If necessary and appropriate, OHRP may also invoke its regulatory authority to delay or suspend such research at other sites pending the outcome of the 407 review process. If the relevant grant application or proposal contains multiple protocols and the IRB or institution refers one protocol to HHS for 407 review, then the awardee institution cannot certify that the entire grant application or proposal has received IRB approval. In such situations, the funding agency could issue a restricted award so that the IRB-approved protocols within the grant can go forward.

OHRP will request written permission from the institution, the IRB, and the principal investigator to allow public review of the grant application, protocol application, parental permission/assent documents, and relevant IRB records. If permission is granted to post the relevant information, OHRP will solicit public review and comment on the proposed research in accordance with the requirements of HHS regulations at 45 CFR 46.407(b). Absent permission to release this information, OHRP may determine that there is not enough information available to the public to allow meaningful comment on the proposed research. Because of OHRP's obligation under the regulations to request public comments before HHS support for the research can be approved, this would effectively halt the 407 review process and the research could not proceed.

Notice of Meeting and Request for Public Comments

A request for written comments will be published in the Federal Register, including an Internet link to the protocol, relevant sections of grant applications, parental permission and assent documents, and relevant excerpts from the IRB minutes and correspondence. In most cases, the total public comment period will last for 60 days after the Federal Register notice has been published. [See timeline for public comment period.]

In addition to requesting public comments on the posted materials, the Federal Register notice will also include the following:

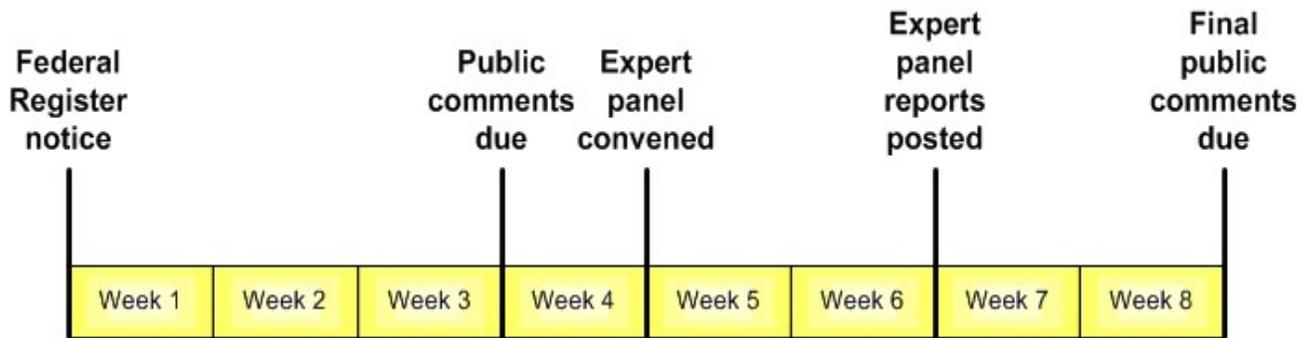
- the date and location of the expert panel meeting (to be held a minimum of four weeks after the notice is posted);
- indication that the panel meeting will be open to the public and that the public will be given an opportunity to comment at the panel meeting;
- a note that written comments on posted materials must be submitted at least one week before the day of the panel meeting to be considered by the panelists (which will allow the public three weeks to comment on posted materials);
- indication that the panelists' reports/recommendations (see below) will be posted two weeks after the panel meets; and
- an invitation to provide comments for up to 30 days after the meeting of the convened panel for review and consideration by OHRP, a summary of which will be transmitted to the Secretary, HHS.

4. Convened OHRP 407 Panel Meeting

All 407 panel meetings will be open to the public. After the convened panel discussion occurs and public comments are received, each panel member will write an independent recommendation as to whether the protocol should proceed, proceed with modifications, or not proceed.

Panel reports will be posted on the OHRP website for informational purposes. The public may continue to provide comments on the protocol and other posted materials for 30 days after the date of the convened panel meeting.

Timeline for 407 Public Comment Period and Expert Panel Review



5. Conclusion of the OHRP Process

Based on panel deliberations, reports, public comments, and its own analysis, OHRP will develop a recommendation within 90 days of the convened panel meeting. Possible outcomes of the 407 review process include:

- HHS approves support of the research as submitted;
- HHS approves support of the research, but with required and/or recommended modifications; **or**
- HHS disapproves support of the research.

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Part 2

Policy No. IV

**Subject: RESEARCH ACTIVITIES INVOLVING COGNITIVELY IMPAIRED PERSONS
AS SUBJECTS**

Rule. Research involving persons whose decision-making capacity may be impaired, should bear some direct relationship to their condition or circumstances.

There are no additional DHHS regulations specifically governing research involving cognitively impaired persons. Although limited decision making capacity should not prevent participation in research, additional scrutiny by the IRB and investigators is applied to research involving this population.

Impaired decision making may range from periods of great stress to severe mental retardation. It is not limited to individuals with psychiatric, neurologic, cognitive or development disorders nor should persons suffering from these conditions be presumed to be decisionally impaired.

- Cognitively impaired - a psychiatric disorder (e.g. psychosis, neurosis, personality disorder or behavior disorders), an organic impairment (e.g. dementia) or developmental disorder (e.g. mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished.
- Competence – the ability to act responsibly on one’s own behalf. In Pennsylvania it has been traditionally separated into two distinct areas, the ability to look after one’s property and the ability to care for one’s self. It is the later area of concern to IRBs. Competence in the absence of a court adjudication is presumed in Pennsylvania even despite a person’s having been involuntarily committed to an institution as being severely mentally disabled.
- Incapacity – similar to competence, person’s mental status indicating inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information and to make a choice. It is the current terminology used in Pennsylvania to signify a person’s incompetence.

A. IRB considerations. (as provided by the NIH Interim report - *Importance of Research Involving Individuals with Impaired Decision-making Capacity.*)

8/13/01

1. The consent process (including consent documents) clearly indicates the differences between individualized treatment and research and between clinician and clinical investigator.
2. Include at least one voting member, independent of the research and investigators, with appropriate professional background, knowledge and experience in working with individuals with questionable capacity.
3. The individual's capacities, impairments, and needs must be taken into account to enable them to participate. Careful consideration of the timing of assessment must be made in order to assure participants vulnerability is at the minimum possible to maximize their ability to assess and appreciate the risks, benefits, and alternatives to participation in the study as it applies to them personally.
4. Where participants decision making capacity may fluctuate during the course of the research, the IRB should evaluate the necessity for ongoing assessment of participant's capacity.
5. Research subject selection should bear some direct relationship to the proposed participants condition or circumstances.

B. Additional considerations. Establishing effective consent with cognitively impaired persons requires that the IRB address the following:

1. The need for appointing an independent monitor to be present when investigators invite persons with potentially impaired decision making capacity to participate in a research study.
2. Evaluation as to whether the individual is capable of executing an informed consent or whether the subject's legally authorized representative/Surrogate should serve as a surrogate for the research decision. If the latter is required, the IRB must establish,
 - a. the basis for the surrogate consent;
 - b. the criteria used in determining that the potential participant failed to possess the necessary mental ability to exercise a reasoned decision to consent;
 - c. the criteria as to who will serve as the surrogate consent provider. (Pennsylvania law allows for next of kin to serve as surrogate decision makers for certain medical procedures. However, in the absence of a court decision specifically authorizing a guardian to authorize medical research for an incapacitated person, the only other sanctioned legal representative would be one appointed under an Advance Directive or Power of Attorney specifically authorizing the power to consent for participation in medical research).
3. Consider the need for investigators to obtain prospective incompetent subjects' "assent" (as obtained in children lacking legal capacity) and whether the individual's refusal to participate in research should override consent given by a legal representative. (The National Commission for the Protection of Human Subjects has recommended that in the case of research involving more than minimal risk, the objection of an adult subject who is incapable of consenting should be binding, unless the individual's participation is specifically authorized by a court of law, the intervention

is expected to provide a direct health benefit to the subject, and the intervention is available only in the context of the research.)

C. Investigator responsibilities.

1. Provide for the inclusion/exclusion of participants with impaired decision making capability in accordance with the direction of the IRB.
2. Obtain informed consent as assessed by the IRB with full regard to the participants capacity to consent and/or need for consent from the appropriate legally authorized representative/Surrogate.

Part 3

ADDITIONAL PROCEDURES FOR SPECIFIC
RESEARCH ACTIVITIES

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Part 3

Policy No. 1

**Subject: RESEARCH ACTIVITIES INVOLVING PATIENT MEDICAL RECORDS AND /
OR PATIENT CHARTS**

Rule. IRB review is required for studies wherein research activities involve obtaining data from patient medical records and/or patient charts that has been collected for nonresearch purposes (such as medical treatment or diagnosis) if these sources are not publicly available or if the information is recorded by the Research Investigator in such a manner that subjects may be identified, directly or through identifiers linked to the subjects. [45CFR 46.101(b)(4)]

The following risk situations raising privacy and/or confidentiality issues are commonly involved in this type of research design:

- there is risk of breach of confidentiality without the knowledge or consent of the patient, or
- there is possibility of contacting patients or their physicians through disclosure of subject responses, or
- there is possibility of recruitment of patients into/to future non-therapeutic studies through disclosure of subject responses.

A. Determination of action. Investigators must submit all intended research studies involving patient medical records and/or patient charts to the ORA. The Director in cooperation with the Chairman will determine the appropriate action to be taken.

B. Determination of IRB review. (See Part 1, Sections V and XI)

1. Full IRB review is required where identification of the subjects and/or disclosure of their responses could reasonably place them at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, insurability, reputation, or be stigmatizing.
2. Expedited review may be used if reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. That is, identifiable information will not be collected or disclosed to anyone other than the investigators at any time present or future.

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Part 3

Policy No. II

**Subject: RESEARCH ACTIVITIES INVOLVING RESIDUAL BODY FLUIDS, TISSUES
AND BODY PARTS**

Rule. IRB review is required for studies wherein research activities involve the utilization of human body fluids, tissues and/or recognizable body parts obtained from operating rooms, clinical settings, pathology laboratories, or morgues regardless when such specimens may be identified, directly or through identifiers linked to the subjects. 45CFR 46.10 1(b)(4)].

A. Determination of action. Investigators must submit all intended research studies using residual body fluid, tissues or body parts to the ORA. The Director in cooperation with the Chairman will determine the appropriate action to be taken.

B. Determination of IRB review.

1. IRB review is required for all studies according to the rule above.
2. Expedited IRB review. Prospective collection of pathological or diagnostic specimens may fall under the expedited review procedure, however, the standard requirements for informed consent (or its waiver, alteration or exception) apply regardless of the type of review - expedited or full - used by the IRB. (See Part 1, Section V, B, 1)
3. Exempt. Research involving the collection or study of pathological specimens or diagnostic specimens may be granted exempt status if certain criteria are met.
 - a. When the specimens are in existence before the project begins, and
 - b. The sources are publicly available or the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

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Part 3

Policy No. III

**Subject: RESEARCH ACTIVITIES INVOLVING HUMAN GENETIC MATERIAL and
DNA BANKING**

Rule. IRB review is required for studies wherein research activities involve the study of tissue involving recombinant DNA and DNA banking..

Genetic research comprises four states:

- (1) pedigree studies (to discover the pattern of inheritance of a disease and to catalog the range of symptoms involved;
- (2) positional cloning studies (to localize and identify specific genes);
- (3) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); and
- (4) gene therapy research (to develop treatments for genetic disease at the DNA level).
Note: the latter category will have a separate section herein.

A. IRB Considerations

Unlike the risks presented by many biomedical research protocols, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subject's insurability and employment opportunities. These psychosocial risks can be significant and warrant careful IRB review.

The fact that many of these studies are limited to family history and information and blood drawing should not, therefore, automatically classify them as "minimal risk" studies qualifying for expedited review.

1. Definitions - Genetic Research

- a. The analysis of human chromosomes or DNA for the purpose of deriving information concerning the presence, absence or mutation of genes, DNA markers, gene products or inherited characteristic; or
- b. measurements of proteins and metabolites to collect and evaluate information regarding the inheritability of diseases and or characteristics in a family.

2. Identifiers - The subject's name, social security number, medical record number, patient number or other trace identifier capable of linking the study subject donor to the specimen.
3. Consideration of source of the tissue of biological specimen.
 - a. Where the tissue or biological specimen is obtained specifically for research purposes - This requires IRB approval as well as the research participant's prior informed consent.
 - b. Where the specimen is a residual sample of tissue removed for clinical treatment and or pathology purposes - This type of tissue source always requires prior IRB approval. However, whether the donor subject must give an informed consent depends upon whether the tissue or specimens have subject identifiers included with the sample or related subject information obtained by the investigators, and/or the investigators have direct access to linkage code information and the investigators can link the tissue samples, subject information and subject identities. (The IRB must be absolutely certain that no identifying linkage exists before it may approve research of this type without informed consent being obtained.)
 - c. Where the tissue is banked or previously collected for pathology specimens or for a different research study - Since this type of research involves gene study, it too requires submission to the IRB for appropriate determination. The same criteria as set forth in b, above must be met before this tissue may be used without the donor subjects informed consent being obtained.

B. OHRP recommendations

It has been recommended by OHRP that research involving the use and storage of specimens for future research projects should have the protocol and consent include a clear description of the following: the operation of the repository where the specimens will be stored, the specific types of research to be conducted, the conditions under which data and specimens will be released to other recipient investigators, if any, the procedures for protecting the privacy of subjects and maintaining confidentiality of data, and the procedures for the subject to withdraw his or her sample from the repository in the future.

C. Informed Consent

The information presented to subjects in the informed consent should be as specific as possible. It should describe the nature and purpose of the research and address the following issues:

1. That their sample, tissue, etc. will be used for genetic research.
2. What procedures will be performed for obtaining the sample.
3. The length of time the samples will be stored.
4. The kind of information they will be provided and when, or that no genetic information will be provided. If no information is to be disclosed, an explanation as to why it is being withheld and whether it may be available in the future.

5. That family members may be included or that information about themselves or their family may be learned which may cause them or their family discomfiture. (Investigators must take precaution so as not to release information concerning one family member to another without first obtaining consent.)
6. Information concerning one family member obtained from another should not be recorded in such a manner so as to be linked to that second person if sensitive in nature without obtaining the consent of the second person.
7. That information about one family member may be learned by another.
8. That information that they learn or information generated about them during the study may compromise their insurability.
9. That actions they may take as a result of their participation may expose them to risks (e.g., such as submitting insurance claims for genetic counseling which are not covered.)
10. The assurances that can be given to protect confidentiality and what if any lack of assurance can be given. The subjects should be informed that their biological sample or genetic material will be under the control of the named investigator or facility.
11. Their rights retained and given up regarding control over what can be done with the tissue they donate. Advise the participants whether or not their biological sample or tissue will be given with or without subject identifiers to secondary investigators (that is, persons other than those involved in the current research study.) Advise participants whether they will be contacted to consent to the secondary use of their biological samples or genetic material.
12. What the consequences of withdrawing from the study will be, and
13. What are any costs associated with participating in the study.

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Part 3

Policy No. IV

**Subject: RESEARCH ACTIVITIES INVOLVING ADMINISTRATION OF GENE
THERAPY (Transfer)**

Rule. IRB review is required for studies involving gene therapy. Preparation of the research protocol and its review by the IRB follow the standard procedures described in Part 1, Sections III and XIII of this manual. Approval to conduct gene therapy research studies at the Main Line Hospital will be determined on a “case by case” basis by the appropriate institutional officials, committees, and the Main Line Hospitals Board of Trustees.

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Part 3

Policy No. V

Subject: SURVEYS

Rule. IRB review is required for studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures when subjects may be identified, directly or through identifiers linked to the subjects.

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Part 3

Policy No. VI

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

Rule. Proposed research studies involving the exposure of human subjects to ionizing radiation must be presented to the Radiation Safety Committee on the appropriate campus which is responsible for evaluating the risks of medical projects involving radiation and limiting the radiation exposure of employees and patients. Exceptions are the use of standard procedures which are:

- (1) diagnostic in routine clinical practice for the purpose of screening subjects and/or evaluating a therapeutic response, or
- (2) therapeutic in the medical management of the patient.

Initial research studies approved by the Radiation Safety Committee may then be presented to the IRB which shall then evaluate the relative risks and benefits of proposals utilizing radioactive materials or X-rays.

The FDA requires investigators to submit an Investigational New Drug Application (IND) for radioactive drugs, kits, or generators that are to be used for investigational diagnostic or therapeutic purposes (including testing to establish their safety and effectiveness). An exception is made for radioactive drugs to be used in certain research designed to study the metabolism of the drug or to gather information about human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes.

A. Definitions.

1. Radioactive drug. Any substance defined as a drug in 201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. (21CFR 310.3(n).

Part 3, Policy VI. RESEARCH ACTIVITIES INVOLVING EXPOSURE OF
RESEARCH SUBJECTS TO IONIZING RADIATION

2. Radioactive Drug Research Committee. An FDA-approved institutional committee, which must be activated if required, responsible for the use of radioactive drugs in human subjects for certain research purposes. Research involving human subjects that proposes to use radioactive drugs must be approved by the RDRC and must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. The research must be basic research, not intended for diagnosis or treatment of a disease. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drug use to ensure that the research continues to comply with FDA requirements, including reporting obligations.
3. Radiopaque Contrast Agents (dyes). Materials that stop or attenuate radiation that is passed through the body, creating an outline on film of the organ(s) being examined. Contrast agents, sometimes called "dyes", do not contain radioisotopes. When such agents are used, exposure to radiation results only from the X-ray equipment used in the examination. The chemical structure of radiopaque contrast agents can produce a variety of adverse reactions, some of which may be severe- and possibly life-threatening - in certain individuals. Risk from radiation exposure results only from the X-ray equipment used in the examination.
4. Radiopharmaceuticals. Radioactive drugs that are labeled or tagged with a radioisotope. These materials are largely physiological or subphysiological in action, and, in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are introduced into the body. Radiation exposure risks are posed by the radioisotope's half-life, the radiosensitivity of the organ system being studied, and the radiation dose to the target organ, adjacent organs, and the whole body.
5. REM. Acronym for Radiation Equivalent in Man; the unit of measurement for a dose of an ionizing radiation that produces the same biological effect as a unit of absorbed dose (1 rad) of ordinary x-rays.

B. IRB considerations.

1. Can the information to be gained from the research project be gathered using methods that do not expose subjects to more radiation than that to which they would naturally be exposed?
2. Could the research be performed on patient undergoing the procedures for diagnostic or therapeutic purpose?
3. Will the smallest exposure (dose) possible be used in the study?
4. Have investigators taken steps to avoid re-exposures in the event that the study needs to be repeated?
5. Have the investigators taken adequate precautions to screen subjects and exclude those not essential to the research project and those at increased risk from exposure

to radiation or contrast agents?

6. Will both men and women be informed of the risks to future offspring due to possible genetic damage?
7. Will women of child-bearing potential be adequately informed of the risks to an embryo associated with radiation exposure in early pregnancy, and of the importance of disclosing a possible pregnancy to the PI? Does the protocol make adequate provisions for detecting pregnancies?

C. IRB duties.

1. Distinguish between radiation exposure resulting from routine medical management of a patient and radiation exposure that is part of research.
2. Determine the level of risk associated with exposure of subjects to radiation
3. Determine what should be told to subjects as part of the informed consent:
 - a. How properly to communicate the uncertainty about the risk of harm posed by exposure to the level of radiation involved in the study. Since subjects must be given sufficient information on which to decide whether to participate, consent should be based on information that the subjects may reasonably be expected to want to know.
 - b. How much risk must there be before a "reasonable volunteer" would want to know about it.
4. Require that subjects be told that participation in the research involves exposure to radiation. May compare with exposure from familiar medical procedures, such as chest X-rays, etc.
5. Ensure that the risks of radiation exposure are minimized.

D. Investigator responsibilities.

1. Submit new research protocol to the IRB following Radiation Safety Committee approval.
2. Obtain consent from participants in accordance with the IRB approved informed consent document.

PART 4

PROCEDURES FOR RECRUITING
RESEARCH SUBJECTS

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Part 4

Policy No. I

Subject: IDENTIFYING RESEARCH SUBJECTS

Rule. IRB review of methods and activities for identifying research subjects is required and must be part of the package for initial review.

A. Using records to identify research subjects.

1. If potential subjects are to be identified through medical records, log books, physicians' records, or other records that are not public documents, the following conditions must be met:
 - a. The investigator is permitted access to such records by the Institution or the subject's physician (who has obtained permission from the patient to release his or her name for contact); and
 - b. The investigator clearly accepts responsibility for confidentiality and privacy.
2. Scanning and/or reviewing of medical or other private records may not be done under any circumstances prior to IRB approval.

B. Using screening tests to identify research subjects.

1. Determining eligibility through use of therapeutic procedures.

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as for diagnosis or treatment of a disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent.

2. Determining eligibility through use of research screening procedures.

Part 4, Policy I. IDENTIFYING RESEARCH SUBJECTS

While investigators may discuss availability of studies and the possibility of entry into a study with a prospective subject without first obtaining informed consent, informed consent must be obtained prior to the initiation of any clinical screening procedures that are performed solely for the purpose of determining eligibility for research.

- a. Screening procedures include withdrawal from medication (wash-out) in anticipation of or in preparation for the research.
 - b. Unless the screening tests involve more than minimal risk or involve a procedure for which written consent is normally required outside the research context, the IRB may decide that prospective study subjects need not sign a consent document.
3. If the screening indicates that the prospective subject is eligible, the informed consent procedures for the study, as approved by the IRB, would then be followed.

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Part 4

Policy No. II

Subject: ADVERTISING FOR RESEARCH SUBJECTS

Rule. IRB review of the purpose of materials and methodology to be used in advertising for research subjects is required to determine that the information contained in the advertisement as well as the mode of its communication, is not misleading to subjects. Advertisements should be part of the package for initial review.

A. Media advertisements. Such advertising is direct advertising which is intended to be seen and heard by prospective subjects to solicit their participation in a research study.

1. Methods and materials to be used by investigators.

- a. Includes, but is not necessarily limited to, the newspaper, radio, TV, Internet, bulletin boards, posters and flyers that are intended for prospective subjects.
- b. Not included are 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.

2. Correct content of advertising.

- a. Any advertisement to recruit subjects should be limited to the information the prospective subjects need to determine their eligibility and interest.
- b. When appropriately worded, the following items may be included:
 - 1) the name and address of the research investigator and/or research facility;
 - 2) the condition under study and/or the purpose of the research;
 - 3) in summary form, the criteria that will be used to determine eligibility

Part 4, Policy II. ADVERTISING FOR RESEARCH SUBJECTS

- for the study;
- 4) a brief list of participation benefits, if any (e.g., a no cost health examination);
 - 5) the time or other commitment required of the subjects; and
 - 6) the location of the research and the person or office to contact for further information.
3. Guidelines to prevent violations in advertising are as follows:
- a. The procedure for recruiting subjects may not be coercive or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
 - b. No claims may be made, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes of the investigation, or that the test article is known to be equivalent or superior to any other drug, biologic or device. The advertisement should not do any of the following:
 - 1) use terms such as "new treatment", "new medication" or "new drug" without explaining the test article is investigational.
 - 2) promise "free medical treatment" when the intent is only to say subjects will not be charged for taking part in the investigation.
 - 3) emphasize the payment or the amount to be paid by such means as larger or bold type.

B. Receptionist scripts. Such advertising is direct advertising by telephone in which the caller (receptionist) follows a script to determine eligibility of prospective subjects for a specific study.

1. Procedures to be used by investigators must be reviewed by the IRB to assure adequate protection of the rights and welfare of the prospective subjects.
2. Information gathered must be appropriately handled and/or disposed of to protect confidentiality and privacy of the prospective subjects' responses and personal data.

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Part 4

Policy No. III

Subject: PAYMENT TO RESEARCH SUBJECTS

Rule. IRB review is required when research subjects are paid since payment for participation in research is considered a recruitment incentive and must be part of the initial review. Payment to research subjects is not considered a benefit.

A. Considerations.

1. Payment may reflect the degree of risk, inconvenience, or discomfort associated with participation, however, it should not be so large - considering the socio-economic status of the proposed subject - as to be overly influential.
2. Neither the amount of payment nor the proposed method and timing of disbursement may involve undue coercion or undue influence.
3. Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study.
4. While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable providing such incentive is not coercive.
5. The amount paid as a bonus for completion should be reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.

B. Requirements.

All information concerning payment, including the amount and schedule of payment(s) must be set forth in the informed consent document and presented at time of initial review.

PART 5
ADMINISTRATIVE PROCEDURES

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Part 5

Policy No. I

Subject: COMMITTEE RECORD KEEPING

The Chairman designates procedures for the maintenance, retention and accessibility of IRB records.

A. Documentation of IRB Activity. Documentation of IRB activities, is maintained and retained for at least three (3) years after completion of research or until the last subject has completed the study or withdrawn participation, whichever is longer. Documents include but are not necessarily limited to:

1. signed consent documents received from Research Investigators.
2. copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports, Amendments, and reports of injuries to subjects.
3. minutes of IRB meetings in sufficient detail to show the names of attendees at the meetings, including alternate members and which primary members for whom they substituted; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; a written summary of the discussion of controverted issues and their resolution; and dissenting reports and opinions. If a member in attendance has a conflicting interest regarding any project, minutes show that this member did not participate in the review, except to provide information requested by the IRB.
4. records of continuing review activities.
5. copies of all correspondence between the IRB and the Research Investigators.
6. a list of IRB members as required by 45 CFR 46.103(b)(3) and 21 CFR 56.115(a)(5).
7. written procedures for the IRB as required by 45 CFR 46.103(b)(4) and 21 CFR 56.108 (a) and (b).
8. statements of significant new findings provided to subjects, as required by 45 CFR 46.116 (b) (5).

9. copies of all correspondence concerning adverse reactions, unexpected serious harm, noncompliance, and suspension or termination.
10. copies of all correspondence with department heads and agencies (OHRP, DHHS, FDA).

B. Inspection of IRB Records. IRB records are kept accessible for inspection and copying by authorized representatives of HHS or FDA, where appropriate, at reasonable times and in a reasonable manner. They may be copied and forwarded to HHS when requested by authorized HHS representatives where appropriate.

C. Records repository. All records shall be maintained in the ORA or other convenient locations.

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Part 5

Policy No. II

Subject: IRB: Internal Quality and Compliance Audits of Research Protocols

Purpose

The purpose of this policy is to—

- 1) Establish and communicate the responsibilities of the IRB and Investigators regarding the objectives process and procedures for conducting internal site audits to ensure compliance with applicable policies and government regulations
- 2) Foster a culture of continuous improvement to promote such compliance;
- 3) Outline how audit results can assist principal investigators in developing their own programs for quality improvement; and
- 4) Provide continuing education opportunities to help correct problems and prevent future occurrences of noncompliance.

Policy

The Main Line Hospitals Institutional Review Board (IRB) is comprised of three Subcommittees, one for each campus of Main Line Hospitals. Each Subcommittee has the full power and authority to act on behalf of the other Subcommittees. The IRB has overall responsibility for protocol and related document review, monitoring the overall conduct and quality assurance of ongoing trials, and fostering quality improvement of clinical research practices. These activities of the IRB serve to ensure the careful and ethical conduct of research in order to protect the rights and welfare of human research subjects and to optimize compliance with Federal regulations, State laws, Main Line Hospitals policies, and the requirements of the approved protocols. The IRB has delegated the administrative functions of the IRB to the Lankenau Institute for Medical Research (LIMR), Office of Research Affairs (ORA). The ORA administration of the IRB includes the monitoring of the quality of clinical research by conducting two types of audits—Routine On-Site Audits and For-Cause Audits. Quality Improvement activities and programs shall be designed to address issues and concerns that arise out of the audit process.

Part 5, Policy II. Internal Quality and Compliance Audits of Research Protocols

Routine On-Site Auditing

Routine on-site audits are a proactive review of the various components of the research process to assess adherence to the protocol and compliance with Federal, State and local regulations and IRB policies. It is a periodic review of a defined number of research records, for a defined period of time. While not triggered by any event or perceived deficiency, it is intended to be comprehensive and should include a comparison of all components of documentation, such as the protocol, source documents, and case report forms to assess compliance, agreement, and validity/accuracy. An audit of this type is intended to help the investigator and research support staff and may help the sponsor by identifying potential problems or deficiencies in the conduct of a study and in so doing provide a focus for continuing education efforts to show how to correct such problems and avoid them in future studies.

For-Cause On-Site Auditing

For-Cause on-site audits are initiated by the IRB through the ORA and in cooperation with the IRB Chairman or the IRB in a response to one of the following events:

1. Investigator has a history of poor adherence to Protocol requirements and/or IRB policies and procedures.
2. Receipt of an internally initiated complaint or concern from a human subject or family member or Main Line Hospitals personnel; or
3. Receipt of an externally initiated complaint from the OHRP, the FDA or Sponsor of a potential protocol violation(s) or regulatory noncompliance(s) the MLH Administrative Policy and Procedure/I.59 shall apply for this type of for cause audit.
4. The IRB shall consult with the MLH Legal Department prior to initiating an audit or engaging and outside auditor for the purpose of determining whether the audit should be performed at the direction of legal counsel.

Procedures**Frequency and Scope of Audits**

The frequency and scope of audits will be determined by the Chairman of the IRB in coordination with the Institutional Official who will be assisted by the ORA .

Individual research studies may be audited on a more frequent, non-routine basis at the direction of a campus Subcommittee of the IRB.

Auditors

Auditors will be appointed by the Institutional Official who may be IRB members and/or independent research auditor(s).

Part 5, Policy II. Internal Quality and Compliance Audits of Research Protocols

Audit Process

1. The studies to be audited as part of Routine On-Site Audits will be selected from a master list, approved by the IRB Chairman and developed by the ORA in cooperation with certain IRB members from each IRB subcommittee.
2. The ORA will notify the Principal Investigator(s) (PI), in writing, a minimum of twenty (20) days prior to the projected timeframe for the audit to arrange a mutually convenient time to conduct the audit.
3. A written notification of the Routine Audit commencement date will be sent to the PI to request all subject records which should include:
 - (a) Case report forms and source documents
 - (b) Informed Consent and Authorization Forms
 - (c) Study protocol and investigator brochure
 - (d) Amendments to protocols and continuing reviews and
 - (e) Study treatment records.
4. The ORA will provide all regulatory records as requested by the auditing team.
5. At the discretion of the auditing team, a brief discussion session will be scheduled with the PI and/or the research staff of each study prior to actual on-site review of documentation. The content of this interview may include but will not be limited to description of some or all of the following:
 - (a) A description of study population and any special needs of the research subjects within this population
 - (b) A description of individuals involved in the conduct of the research and delegation of duties
 - (c) A brief scenario of the recruitment and consent processes
 - (d) The storage and confidentiality of research records / data
 - (e) The process for reporting of Adverse Events
 - (f) A description of how research results will be shared and who might have access to audit results and information
6. The auditing team, at their discretion, may inspect research records for the presence of the following:
 - (a) A valid, legally effective consent with appropriate documentation procedures,
 - (b) Recruitment of subjects with respect to protocol-specific inclusion/exclusion criteria,
 - (c) Documentation of screening tests and laboratory results,
 - (d) Documentation of appropriate subject monitoring and clinic visits,
 - (e) Documentation of adverse events and submission to IRB for review,
 - (f) Clinical and/or departmental Standard Research Operating Procedures,
 - (g) Research record storage and data handling practices,
 - (h) Where investigational drugs and/or devices are part of the research studies, match accountability identified by the principal investigator with all IRB submissions, and

- (i) Where behavioral and social science research studies are evaluated, match on-site documentation to the IRB-approved protocol.
7. The Principal Investigator shall be asked to provide a space for the review of research documents, and arrange for both the PI and his/her research staff to be available during the audit to assist with answers to questions regarding the conduct of the research.
8. Upon completion of the audit, the audit team shall submit a report that outlines all audit findings and recommendations.
9. Auditors will conduct an Exit Interview with the PI at the conclusion of the audit to discuss their findings.

Disclosure of Audit Results and Reports

The auditing team will produce a written report of the audit findings within three (3) weeks of the completion of the audit. The report shall be submitted to the ORA. The ORA will distribute a copy of the report to the Institutional Official and the Chairman of the IRB. The ORA in cooperation with the IRB Chairman, will distribute the report to the appropriate subcommittee(s) of the IRB and the specific sections of the report to the Principal Investigators pertaining to their research protocols.

If protocol violations are found that may place human subjects at risk, the audit team will immediately report the violations to the IRB Chairman, the Institutional Official and the ORA. The IRB Chairman and the Institutional Official, in consultation with the ORA, may suspend the protocol pending review by the appropriate subcommittee of the IRB. Additional requirements for reporting such violations to the Sponsor and/or applicable government agencies will be reviewed and compliance with any such reporting requirements implemented without delay.

Responding to Audits

The appropriate IRB subcommittee as determined by the IRB Chairman will review all audit findings and if found to be adverse in the opinion of the IRB, the PI will be allowed two (2) weeks to respond to the IRB. If the IRB then affirms its final findings, there is no further appeal.

The IRB may also suggest non-mandatory improvements to the PI. In this situation, the IRB will distinguish between formal findings, which are mandatory, and non-mandatory recommendations.

Confidentiality

Audit procedures, results and reports shall be confidential and shall only be distributed to those persons listed in the paragraph above, unless otherwise required by law. The Audit procedures, results and reports are subject to the Main Line Hospitals Confidentiality Policies and Procedures. Any auditor who is not an employee of the ORA or Main Line Hospitals must sign a Main Line Health Business Associate Agreement and any other confidentiality agreements that may be required.

Origination Date: 8-25-05

Revision

Date: Review

Date:

Previous Revision Date:

Key Contact: MLH Legal & IRB Office of Research Affairs

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Approved 9/8/05 by Joint Conference Committee

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ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD

Part 5

Policy No. III

Subject: INTERNAL MONITORING FOR ENSURING COMPLIANCE

The ORA in cooperation with the Chairman, conducts routine self-regulatory practices designed to ensure compliance with Federal Regulations as well as IRB decisions, conditions and requirements.

Rule: The ORA has the authority to ensure compliance with Federal Regulations as well as its decisions, conditions and requirements.

A. Initial review.

1. Standardizing protocol and consent document preparation for ensuring submission of an acceptable research study package to the IRB for initial review.
2. Requiring through these PROCEDURES that all research investigators proposing research first obtain from the ORA the appropriate information for initial protocol submission.
 - a. the forms:
 - 1) Form 001 – Protocol Submission Form
 - 2) Form 002 - Request for INITIAL Review of Research Project Involving Human Subjects

B. Continuing Review.

1. Standardizing Progress Report preparation for ensuring submission of an acceptable package to the IRB for continuing review.
2. Requiring use of the form, Continuing Review Form (Form 003), which is the face sheet for a Progress Report when the study is due for continuing review.

C. Research Investigator Reporting to the IRB.

1. Standardizing forms for investigator reporting to ensure submission of acceptable reports to the IRB for adverse events, serious harm, and changes to protocol and/or consent documents.

Part 5, Policy III. INTERNAL MONITORING FOR ENSURING COMPLIANCE

D. Currently Approved Consent Document Use.

1. Using an official dated approval stamp on the consent document when reviewed for distinguishing the only currently approved document and ensuring its use by research investigators.
2. Requiring submission of the consent document being used as an addition with the submission of Progress, Adverse, and Amendment Reports to monitor and ensure use by research investigators of only the currently approved document.

E. Using written notification letters to investigators which are standardized to include instructions as to their reporting responsibilities for ensuring complete awareness of their duties.

F. Keeping a database calendar for tracking protocols for ensuring timeliness of reporting.

G. Keeping an IRB membership meeting list to track member attendance for ensuring acceptable performance of duties.

H. Performing random audits of approved, ongoing studies for ensuring compliance with the Federal Regulations as well as IRB decisions, conditions and requirements.

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL
MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 5

Policy No. IV

Subject: Jurisdiction Over Clinical Research

I. 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 as research subjects 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 individuals¹⁴ and/or institutions may conduct research at the Main Line Health System.

II. Procedure

Main Line Health System Engagement

The research conducted throughout the Main Line Health (MLH) System is divided into two general 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 IRB¹⁵

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 organization¹⁶
2. **Research in which funding is received or administered by, or contracted with Lankenau Institute for Medical Research (LIMR) or other MLH Affiliate.** This 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.

¹⁴ Refer to footnote 6 for additional information.

¹⁵ In limited circumstances, the MLH IRB may consider entering into an IRB authorization agreement for review by an external IRB.

¹⁶ Main Line Hospitals, Inc., if not referenced separately in this policy, is included among MLH Affiliates.

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 prospective 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

1. **Physicians who lease office space in a medical office building located on one of the Main Line Hospitals (or other MLH Affiliate) campuses.** This category includes research studies that are conducted exclusively in a physician’s office¹⁷, 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, aside from medical staff membership, is that the physician leases space in a building located on a Main Line Hospitals or MLH Affiliate campus. Main Line Health or a MLH Affiliate is not engaged¹⁸ in the research and review by the MLH IRB is optional and voluntary and an external IRB may review the research.

III. Process

The Office of Research Affairs, Lankenau Institute for Medical Research is responsible for, among other activities related to medical 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 Office of Research Affairs shall make the final determination.

A. MLH IRB Fees

Research reviewed by the MLH IRB which is sponsored by industry or grant, excluding federally sponsored research, is subject to a fee.

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 II. B.1., 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.*

¹⁷Research that is conducted by non-employees at non-MLH locations (not owned by Main Line Health, Main Line Hospitals or other MLH Affiliate) are not covered under the Main Line Hospitals Federalwide Assurance.

¹⁸Refer to OHRP Guidance on Engagement of Institutions in Human Subjects Research for a complete discussion on engagement of institutions and individuals in research.

*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	
<p>*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).</p> <p>**Refer to Section II, Category A.2, above for more information.</p> <p>*** Nursing Research requires the signature of appropriate Nurse Manager and/or supervisor.</p>					

IV. Other

Research conducted by non-affiliated¹⁹ 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.

**PART 5, POLICY IV
REVISED 10/01/12**

¹⁹The 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).

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**ADMINISTRATIVE POLICY AND PROCEDURE MANUAL MAIN
LINE HOSPITALS INSTITUTIONAL REVIEW BOARD**

Part 5

Policy No. V

**Subject: MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD (MLH IRB)
POLICY FOR RESPONDING TO ALLEGATIONS OF NON-COMPLIANCE IN A
CLINICAL INVESTIGATION**

Purpose

The purpose of this policy is to provide a standard procedure for inquiry into allegations of non-compliance with federal, state, or local regulations for the protection of human research subjects in a clinical investigation conducted at Main Line Hospitals, Inc.

Inquiry

The Signatory Official (Institutional Official), as designated on the Main Line Hospitals, Inc. Federalwide Assurance, will appoint an Inquiry Committee and Committee Chair within ten days of written notification of the allegation(s) of non-compliance.

The Signatory Official will notify the Principal Investigator and Co-investigator(s) in writing of the allegations and that an inquiry into the allegations is being initiated. Simultaneous with this notification, the Signatory Official or the Signatory Official's designee will sequester all research records relating to the clinical investigation including progress notes, the Physician Operations Manual, and pertinent information entered into patient medical charts. If the Principal Investigator and/or Co-investigator(s) are not available, the collection of these materials may begin in their absence. The Principal Investigator and Co-investigator(s) should not be given notice in advance of the sequestration of these study materials in order to prevent questions being raised later regarding missing documents or materials and to prevent accusations against the Principal and Co-investigator(s) of tampering with or fabricating data or materials after notification of the inquiry. Upon request, a copy of the sequestered materials will be provided to the Principal and Co-investigator by the Office of Research Affairs as soon as practicable.

Part 5, Policy V. MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD (MLH IRB)
POLICY FOR RESPONDING TO ALLEGATIONS OF NON-COMPLIANCE IN A
CLINICAL INVESTIGATION

1. Inquiry Committee

The Committee should consist of the Director of Research Affairs and at least six (6) additional individuals who do not have real or apparent conflicts of interest in the case, are unbiased, and have the necessary expertise to evaluate the evidence and issues related to the allegation(s), interview key individuals to the allegations, and conduct the inquiry. These individuals may be scientists, clinicians, administrators, lawyers, or other qualified persons from inside or outside the institution and must include at least one non-scientific member not affiliated with the institution. Representatives from Main Line Hospitals legal department can appear at meetings as observers but not as a voting member of the Committee because of an inherent conflict of interest.

The Signatory Official, in consultation with the Chair, will determine whether additional experts from inside or outside the institution, other than those appointed to the committee, need to be consulted during the inquiry to provide special expertise to the committee regarding the analysis of specific evidence or information. In this case, the expert(s) provides strictly advisory function to the committee, does not vote, and does not interview the key individuals.

2. Bias or Conflict of Interest

The Signatory Official will take reasonable steps to ensure that the members of the committee and experts have no bias or personal or professional conflict of interest with the key individuals or the case in question. In making this determination, the Signatory Official will consider whether these individuals have:

- financial involvement in the project or with the key individuals,
- co-authored a publication with key individuals in the project,
- collaborated with any of the key individuals in the project,
- a supervisor or mentor relationship with the key individuals,
- a special relationship such as a close personal friendship,
- cause to compromise an individual's objectivity.

Members of the Committee will be requested to sign a conflict of interest statement.

3. Confidentiality

Members of the committee and experts will agree in writing to observe the confidentiality of the proceeding and any information or documents reviewed as part of the inquiry. Outside of the confines of the committee, the members may not discuss the business of the committee in conducting the inquiry with the Principal or Co-investigator or anyone not authorized by the Signatory Official to have knowledge of the inquiry.

4. Charge to the Committee

At the first meeting of the Committee, the Signatory Official will state the charge to the committee, discuss the allegations and related issues, and the appropriate procedures for conducting the inquiry as well as answer questions raised by the committee.

5. Administrative Support

Part 5, Policy V. MAIN LINE HOSPITALS INSTITUTIONAL REVIEW BOARD (MLH IRB)
POLICY FOR RESPONDING TO ALLEGATIONS OF NON-COMPLIANCE IN A
CLINICAL INVESTIGATION

The Office of Research Affairs will provide administrative support in (1) preparing information and distributing it to committee members, (2) maintaining an inventory of records pertinent to the inquiry, (3) recording minutes of the meetings and (4) preparing the inquiry report.

6. Interviews

Principal Investigators, Co-investigators and other individuals to be interviewed should be asked to provide in advance any relevant information including their notes, research records, or other documents that were not sequestered previously but are relevant to the allegation(s). These individuals will be asked by the committee to provide a written account of their involvement in the allegations as well as their response to the allegation(s) at some time during the inquiry but prior to the interview.

Interviewees may be accompanied and advised by legal counsel or other advisors, but they may not participate directly in the interview. Interviewees may communicate with their advisor(s), but the advisor(s) will have no interactive role with the Committee. Interviewees must respond directly to the interview questions.

Inquiry Report

An inquiry report will be prepared by the Committee according to the timeline established by the agency that has given written notice of the allegations. If no timeline has been given, the inquiry report will be issued by the Committee within sixty days following the date of appointment of the Inquiry Committee by the Signatory Official. The report will include the (1) name and title of the committee members and experts, (2) allegations, (3) description of financial support for the clinical investigation, (4) description of the inquiry process, (5) a list of research records and documents pertinent to the inquiry, (6) descriptive response with reference to appropriate documentation to each allegation in sufficient detail to support the determination made by the Committee, (7) specific reporting requirements of the agency requesting the inquiry, and (8) the determination of the Committee for each allegation. The Signatory Official will sign the report and forward it via the Office of Research Affairs to the agency requesting the inquiry.

A copy of the Inquiry Report is maintained in the archives of the Office of Research Affairs. Additional copies are distributed to the Signatory Official, the Principal Investigator and Co-investigator(s), the Department Chairman/Division Chief, the President of Main Line Hospitals, Inc, and the Main Line Hospitals Legal Department. Either a copy of the report or a summary of the determinations of the Committee as determined by the Signatory Official in consultation with the Chair will be provided to the IRB subcommittee that originally reviewed/approved the clinical investigation.

GLOSSARY OF TERMS

ABUSE-LIABLE - Pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both illicit drugs (e.g., heroine) and licit drugs (e.g., methamphetamines).

ACT - Term meaning the Federal food, Drug, and Cosmetic Act, as amended.

ADJUVANT THERAPY - Therapy provided to enhance the effect of a primary therapy; auxiliary therapy.

ADVERSE EFFECT - An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy).

ASSENT - Agreement by an individual not competent to give legally valid informed consent (e.g., a child or cognitively impaired person) to participate in research. [45 CFR 46.402(b)]

ASSURANCE - A formal written, binding commitment that is submitted to a federal agency in which an institution promises to comply with applicable regulations governing research with human subjects and stipulates that procedures through which compliance will be achieved. [Federal Policy's 45CFR 46.103].

AUTHORIZED INSTITUTIONAL OFFICIAL - An officer of an institution with the authority to speak for and legally commit the institution to adherence to the requirements of the federal regulations regarding the involvement of human subjects in biomedical and behavioral research.

AUTONOMY - Personal capacity to consider alternatives, make choices, and act without undue influence or interference of others.

BELMONT REPORT - A statement of basic ethical principles governing research involving human subjects issued by the National Commission for the Protection of Human Subjects in 1978.

BENEFICENCE - An ethical principle discussed in the Belmont Report that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do not harm; and (2) protect from harm by maximizing possible benefits and minimizing possible risks of harm.

BENEFIT - A valued or desired outcome; an advantage.

BIOLOGIC - Any therapeutic serum, toxin, anti-toxin, or analogous microbial product applicable to the prevention, treatment, or cure of diseases or injuries.

CADAVER - The body of a deceased person.

CASE-CONTROL STUDY - A study comparing persons with a given condition or disease (the cases) and persons without the condition or disease (the controls) with respect to antecedent factors. (See also: Retrospective Studies).

CAT SCAN - Abbreviation for Computerized Axial Tomography, an X-ray technique for producing images of internal bodily structures through the assistance of a computer.

GLOSSARY OF TERMS

CHILDREN - Persons who have not attained legal age for consent to treatment or procedures involved in the research, as determined under the applicable law of the jurisdiction in which the research will be conducted [45 CFR 46.402(a)].

CDC - Centers for Disease Control and Prevention; an agency within the Public Health Service, Department of Health and Human Services.

CLASS I, II, III DEVICES - Classification by the Food and Drug Administration of medical devices according to potential risks or hazards.

CLINICAL INVESTIGATION - Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505 (i), 507(d), or 520(g) of the act, or is not subject to requirements for prior submission to the FDA under these actions of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of the chapter regarding non clinical laboratory studies.

CLINICAL TRIAL - A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or of behavioral interventions.

COGNITIVELY IMPAIRED - Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behavior disorders, or dementia) or a developmental disorder (e.g., mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

COHORT - A group of subjects initially identified as having one or more characteristics in common who are followed over time. In social science research, this term may refer to any group of persons who are born at about the same time and share common historical or cultural experiences.

COMPENSATION - Payment or medical care provided to subjects injured in research; does not refer to payment (remuneration) for participation in research.

COMPETENCE - Technically a legal term, used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

CONFIDENTIALITY - Pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure.

CONSENT - See Informed Consent.

CONTRACT - An agreement; as used here, an agreement that a specific research activity will be performed at the request, and under the direction, of the agency providing the funds. Research performed under contract is more closely controlled by the agency than research performed under a grant.

GLOSSARY OF TERMS

CONTROL SUBJECTS or CONTROLS - Subject(s) used for comparison who are not given a treatment under study or who do not have a given condition, background, or risk factor that is the object of study. Control conditions may be concurrent (occurring more or less simultaneously with the condition under study) or historical (preceding the condition under study). When the present condition of subjects is compared with their own condition on a prior regimen or treatment, the study is considered historically controlled.

CONTRAINDICATED - Disadvantageous, perhaps dangerous; a treatment that should not be used in certain individuals or conditions due to risks (e.g., a drug may be contraindicated for pregnant women and persons with high blood pressure).

CROSS-OVER DESIGN - A type of clinical trial in which each subject experiences, at different times, both the experimental and control therapy. For example, half of the subjects might be randomly assigned first to the control group and then to the experimental intervention, while the others would have the sequence reversed.

DATA AND SAFETY MONITORING BOARD - A committee of scientists, physicians, statisticians, and others that collects and analyzes data during the course of a clinical trial to monitor for adverse effects and other trends (such as an indication that one treatment is significantly better than another, particularly when one arm of the trial involves a placebo control) that would warrant modification or termination of the trial or notification of subjects about new information that might affect their willingness to continue in the trial.

DEAD FETUS - An expelled or delivered fetus that exhibits no heartbeat, spontaneous respirator activity, spontaneous movement of voluntary muscles, or pulsation of the umbilical cord (if still attached) [45 CFR 46.203(f)]. Generally some organs, tissues, and cells (referred collectively as fetal tissue) remain alive for varying periods of time after the total organism is dead.

DEBRIEFING - Giving subjects previously undisclosed information about the research project following completion of their participating in research. (Note that this usage, which occurs within the behavioral sciences, departs from standard English, in which debriefing is obtained rather than imparting information).

DECLARATION OF HELSINKI - A code of ethics for clinical research approved by the World Medical Association in 1964 and widely adopted by medical associations in various countries. It was revised in 1975 and 1989.

DEPENDENT VARIABLES - The outcomes that are measured in an experiment. Dependent variables are expected to change as a result of an experimental manipulation of the independent variable(s).

DESCRIPTIVE STUDY - Any study that is not truly experimental (e.g., quasi-experimental studies, correlational studies, record review, case histories, and observational studies).

DHHS - A federal agency: U.S. Department of Health and Human Services; formerly the Department of Health, Education and Welfare (DHEW).

DIAGNOSTIC PROCEDURE - Test used to identify a disorder or disease in a living person.

GLOSSARY OF TERMS

DOUBLE-MASKED DESIGN - A study design in which neither the Research Investigators nor the subjects know the treatment group assignments of individual subjects. Sometimes referred to as “double blind”.

DRUG - Any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or other abnormal conditions.

EMANCIPATED MINOR - A legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law (for such purposes as consenting to medical care), but who are entitled to treatment as if they had by virtue of assuming adult responsibilities such as being self-supporting and not living at home, marriage, or procreation. (See also: Mature Minor).

EMBRYO - Early stages of a developing organism, broadly used to refer to stages immediately following fertilization of an egg through implantation and very early pregnancy (i.e., from conception to the eighth week of pregnancy).

EPIDEMIOLOGY - A scientific discipline that studies the factors determining the causes, frequency, and distribution of diseases in a community or a given population.

EQUITABLE - Fair or just; used in the context of selection of subjects to indicate that the benefits and burdens of research are fairly distributed [Federal Policy s46.111(a)(3)].

ETHICS ADVISORY BOARD - An interdisciplinary group that advises the Secretary, HHS, on general policy matters and on research proposals (or classes of proposals) that pose ethical problems.

EXPANDED AVAILABILITY - Policy and procedure that permits individuals who have life-threatening diseases for which there are no alternative therapies to have access to investigational drugs and devices that may be beneficial to them. Examples of expanded availability mechanisms include Treatment INDs, Parallel Track, and open study protocols.

EXPEDITED REVIEW - Review of proposed research by the IRB chair or a designated voting member or group of voting members rather than by the entire IRB. Federal rules permit expedited for certain kinds of research involving no more than minimal risk and for minor changes in approved research [Federal Policy s46.110].

EXPERIMENTAL - Term often used to denote a therapy (drug, device, procedure) that is unproven or not yet scientifically validated with respect to safety and efficacy. A procedure may be considered “experimental” without necessarily being part of a formal study (research) to evaluate its usefulness. (See also: Research).

EXPERIMENTAL STUDY - A true experimental study is one in which subjects are randomly assigned to groups that experience carefully controlled interventions manipulated by the experimenter according to a strict logic allowing casual inference about the effects of the intervention under investigation. (See also: Quasi-Experimental Study).

FDA - Food and Drug Administration; an agency of the federal government established by Congress in 1923 and presently part of the Department of Health and Human Services.

GLOSSARY OF TERMS

FEDERAL POLICY (THE) - The federal policy that provides regulations for the involvement of human subjects in research. The Policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the Policy applicable to such research. Currently, sixteen federal agencies have adopted the Federal Policy.

FETAL MATERIAL - The placenta, amniotic fluid, fetal membranes, and umbilical cord.

FETUS - The product of conception from the time of implantation until delivery. If the delivered or expelled fetus is viable, it is designated an infant [45 CFR 46.203(c)].

FIELDWORK - Behavioral, social, or anthropological research involving the study of persons or groups in their own environment and without manipulation for research purposes (distinguished from laboratory or controlled settings).

501 (K) DEVICE - A medical device that is considered substantially equivalent to a device that was or is being legally marketed. 501 (k) is the section of the Food, Drug and Cosmetic Act that describes pre-market notification; hence the designation "501(k) device".

FULL BOARD REVIEW - Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary interests are in nonscientific areas. For research to be approved, it must receive the approval of a majority of those members present at the meeting [Federal Policy s46.108].

GENE THERAPY - The treatment of genetic disease accomplished by altering the genetic structure of either somatic (nonreproductive) or germline (reproductive) cells.

GENOTYPE - The genetic constitution of an individual.

GRANT - Financial support provided for research study designed and proposed by the principal Research Investigator(s). The granting agency exercises no direct control over the conduct of approved research supported by a grant.

GUARDIAN - An individual who is authorized under applicable state or local law to give permission on behalf of a child to general medical care [45 CFR 46.402(e)].

HUMAN IN VITRO FERTILIZATION - Any fertilization involving human sperm and ova that occurs outside the human body.

HUMAN SUBJECT - (Per FDA) An individual who is or becomes a participant in research, either as recipient of the test article or as a control. A subject may be either a healthy human or a patient.

(Per HHS) Individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project.

(Per federal regulations) A living human being from whom an Research Investigator obtains data through intervention or interaction with the subject or obtains identifiable private information [Federal Policy s46.102(f)].

IDE - See: Investigational Device Exemptions.

GLOSSARY OF TERMS

INCAPACITY - Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice.

INCOMPETENCE - Technically, a legal term meaning inability to manage one's own affairs.

INFORMED CONSENT - A person's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure. In giving informed consent, subjects may not waive or appear to waive any of their legal rights, or release or appear to release the Research Investigator, the sponsor, the institution or agents thereof from liability for negligence [Federal Policy s116; 21 CFR 50.20 and 50.25].

INSTITUTION - Term "Institution" is used within this document to signify The Main Line Hospitals, Inc.

INSTITUTIONAL REVIEW BOARD (IRB) - A specially constituted review body established or designated by an entity to protect the welfare of human subjects recruited to participate in biomedical or behavioral research [Federal Policy ss46.102(g), 46.108, 46.109].

INSTITUTIONALIZED - Confined, either voluntarily or involuntarily (e.g., a hospital, prison, or nursing home).

INSTITUTIONALIZED COGNITIVELY IMPAIRED - Persons who are confined, either voluntarily or involuntarily, in a facility for the care of the mentally or otherwise disabled (e.g., a psychiatric hospital, home or school for the retarded).

INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) - Exemptions from certain regulations found in the Medical Device Amendments that allow shipment of unapproved devices for use in clinical investigations [21 CFR 812.20].

INVESTIGATIONAL NEW DRUG OR DEVICE - A drug or device permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing.

IN VITRO - Literally, "in glass" or "test tube"; used to refer to processes that are carried outside the living body, usually in the laboratory, as distinguished from *in vivo*.

IN VIVO - Literally, "in the living body"; processes, such as the absorption of a drug by the human body, carried out in the living body rather than in a laboratory (*in vitro*).

IRB - See Institutional Review Board.

JUSTICE - An ethical principle discussed in the Belmont Report requiring fairness in distribution of burdens and benefits; often expressed in terms of treating persons of similar circumstances similarly.

LACTATION - The period of time during which a woman is providing her breast milk to an infant or child.

GLOSSARY OF TERMS

LEGALLY AUTHORIZED REPRESENTATIVE/SURROGATE - A person authorized either by statute or by court appointment to make decisions on behalf of another person. In human subjects research, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [Federal Policy s46.102(c)].

LONGITUDINAL STUDY - A study designed to follow subjects forward through time.

MASKED STUDY DESIGNS - Study designs comparing two or more interventions in which either the Research Investigators, the subjects, or some combination thereof do not know the treatment group assignments of individual subjects. Sometimes called "blind" study designs. (See also: Double-Masked Design; Single-Masked Design).

MATURE MINOR - Someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessarily an emancipated minor. (See also: Emancipated Minor).

MEDICAL DEVICE - A diagnostic or therapeutic article that does not achieve any of its principal intended purpose through chemical action within or on the body. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, and orthopedic pins or other orthopedic equipment.

MEDICAL DEVICE AMENDMENTS (MDA) - Amendments to the Federal Food, Drug and Cosmetic Act passed in 1976 to regulate the distribution of medical devices and diagnostic products.

MENTALLY DISABLED - See: Cognitively Impaired.

METABOLISM (OF A DRUG) - The manner in which a drug is acted upon (taken up, converted to other substances, and excreted) by various organs of the body.

MINIMAL RISK - A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed 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 [Federal Policy s46.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examinations. The definition of minimal risk for research involving prisoners differs somewhat from that given for noninstitutionalized adults. [See 45 CFR 46.303(d) and Guidebook Chapter 6, Section E, "Prisoners".]

MONITORING - The collection and analysis of data as the project progresses to assure the appropriateness of the research, its design and subject protections.

NDA - See New Drug Application.

NEW DRUG APPLICATION - (NDA) Request for FDA approval to market a new drug.

GLOSSARY OF TERMS

NIH - National Institutes of Health; a federal agency within the Public Health Service, DHHS, comprising 21 institutes and centers. It is responsible for carrying out and supporting biomedical and behavioral research.

NIMH - National Institutes of Mental Health; an institute in NIH.

NONAFFILIATED MEMBER - Member of an Institutional Review Board who has no ties to the parent institution, its staff, or faculty. This individual is usually from the local community (e.g., minister, business person, attorney, teacher, homemaker).

NONSIGNIFICANT RISK DEVICE - An investigational medical device that does not present significant risk to the patient. (See also: Significant Risk Device).

NONTHERAPEUTIC RESEARCH - Research that has no likelihood or intent of producing a diagnostic, preventive, or therapeutic benefit to the current subjects, although it may benefit subjects with a similar condition in the future.

NONVIABLE FETUS - An expelled or delivered fetus which, although it is living, cannot possible survive to the point of sustaining life independently, even with the support of available medical therapy [45 CFR 46.203(d) and (e)]. Although it may be presumed that an expelled or delivered fetus is nonviable at a gestational age less than 20 weeks and weight less than 500 grams [Federal Register 40 (August 8, 1975): 33552], a specific determination as to viability must be made by a physician in each instance.

NORMAL VOLUNTEERS - Volunteer subjects used to study normal physiology and behavior or who do not have the condition under study in a particular protocol, used as comparisons with subjects who do have the condition. "Normal" may not mean normal in all respects. For example, patients with broken legs (if not on a medication that will affect the results) may serve as normal volunteers in studies of metabolism, cognitive development, and the like. Similarly, patients with heart disease but without diabetes may be the "normals" in a study of diabetes complicated by heart disease.

OFFICE FOR HUMAN RESEARCH PROTECTION (OHRP) - The office within the National Institutes of Health, an agency of the Public Health Service, Department of Health and Human Services, responsible for implementing DHHS regulations (45 CFR Part 46) governing research involving human subjects.

OPEN DESIGN - An experimental design in which both the Research Investigator(s) and the subjects know the treatment group(s) to which subjects are assigned.

PATERNALISM - Making decisions for others against or apart from their wishes with the intent of doing them good.

PERMISSION - The agreement of parent(s) or guardian to the participation of their child or ward in research [45 CFR 46.402(c)].

PHARMACOLOGY - The scientific discipline that studies the action of drugs on living systems (animal or human beings).

GLOSSARY OF TERMS

PHASE 1, 2, 3, 4 DRUG TRIALS - Different stages of testing drugs in humans, from first application in humans (Phase 1) through limited and broad clinical tests (Phase 3), to postmarketing studies (Phase 4).

PHASE 1 DRUG TRIAL - Phase 1 trials include the initial introduction of an investigational new drug into humans. These studies are typically conducted with healthy volunteers; sometimes, where the drug is intended for use in patients with a particular disease, however, such patients may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled, sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

PHASE 2 DRUG TRIAL - Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in patients with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with a relatively small number of patients, usually involving no more than several hundred subjects.

PHASE 3 DRUG TRIAL - Phase 3 trials involve the administration of a new drug to a larger number of patients in different clinical settings to determine its safety, efficacy, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand patient-subjects.

PHASE 4 DRUG TRIAL - Concurrent with marketing approval, FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were in Phase 2 studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time [21 CFR 312.85].

PHENOTYPE - The physical manifestation of a gene function.

PHS - Public Health Service. Part of the U.S. Department of Health and Human Services, it includes FDA, NIH, CDC, SAMHSA, and HRSA.

PLACEBO - A chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug.

GLOSSARY OF TERMS

POSTAMENDMENTS DEVICES - Medical devices marketed after enactment of the 1976 Medical Device Amendment.

PREAMENDMENTS DEVICES - Medical devices marketed before enactment of the 1976 Medical Device Amendment.

PRECLINICAL INVESTIGATION - Laboratory and animal studies designed to test the mechanisms, safety, and efficacy of an intervention prior to its applications to humans.

PREDICATE DEVICES - Currently legally marketed devices to which new device may be found substantially equivalent under the 510(k) process.

PREGNANCY - The period of time from confirmation of implantation of a fertilized egg within the uterus until the fetus has entirely left the uterus (i.e., has been delivered). Implantation is confirmed through a presumptive sign of pregnancy such as missed menses or a positive pregnancy test [45 CFR 46.203(b)]. This “confirmation” may be in error, but, for research purposes, Research Investigators would presume that a living fetus was present until evidence to the contrary was clear. Although fertilization occurs a week or more before implantation, the current inability to detect the fertilization event or the presence of a newly fertilized egg makes a definition of pregnancy based on implantation necessary.

PRINCIPAL RESEARCH INVESTIGATOR - The scientist or scholar with primary responsibility for the design and conduct of a research project.

PRISONER - An individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures that provide alternatives to criminal prosecution or incarceration in penal institution, and individuals detained pending arraignment, trial or sentencing.

PRIVACY - Control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others.

PROPHYLACTIC - Preventive or protective; a drug, vaccine, regimen or device designed to prevent, or provide protection against, a given disease or disorder.

PROSPECTIVE STUDIES - Studies designed to observe outcomes or events that occur subsequent to the identification of the group of subjects to be studied. Prospective studies need not involve manipulation or intervention but may be purely observational or involve only the collection of data.

PROTOCOL - The formal design or plan of an experiment of research activity; specifically, the plan submitted to an IRB for review and to an agency for research support. The protocol includes a description of the research design or methodology to be employed, the eligibility requirements for prospective subjects and controls, the treatment regimen(s), and the proposed methods of analysis that will be performed on the collected data.

QUASI-EXPERIMENTAL STUDY - A study that is similar to a true experimental study except that it lacks random assignments of subjects to treatment groups.

GLOSSARY OF TERMS

RADIOACTIVE DRUG - Any substance defined as a drug in s201(b)(1) of the Federal Food, Drug and Cosmetic Act that exhibits disintegration of unstable nuclei with the emission of nuclear particles or photons. [21 CFR 310.3(n)]

RADIOACTIVE DRUG RESEARCH COMMITTEE - The Main Line Hospitals, Inc. committee responsible for the use of radioactive drugs in human subjects for research purposes. Research involving human subjects that purposes to use radioactive drugs must meet various FDA requirements, including limitations on the pharmacological dose and the radiation dose. Furthermore, the exposure to radiation must be justified by the quality of the study and the importance of the information it seeks to obtain. The committee is also responsible for continuing review of the drugs to ensure that the research continues to comply with FDA requirements, including reporting obligations.

RADIOPAQUE CONTRAST AGENTS - Materials that stop or attenuate radiation that is passed through the body, creating an outline on film of the organ(s) being examined. Contrast agents, sometimes called “dyes”, do not contain radioisotopes. When such agents are used, exposure to radiation results only from the x-ray equipment used in the examination. The chemical structure of radiopaque contrast agents can produce a variety of adverse reactions, some of which may be severe - and possibly life-threatening - in certain individuals.

RADIOPHARMACEUTICALS - Drugs (compounds or materials) that may be labeled or tagged with a radioisotope. These materials are largely physiological or subpharmacological in action, and in many cases, function much like materials found in the body. The principal risk associated with these materials is the consequent radiation exposure to the body or to specific organ systems when they are injected into the body.

RANDOM, RANDOM ASSIGNMENT, RANDOMIZATION, RANDOMIZED - Assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically (e.g., as dictated by the standard or usual response to their condition, history, or prognosis, or according to demographic characteristics). Random assignment of subjects to conditions is an essential element of experimental research because it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention.

REMISSION - A period in which the signs and symptoms of a disease are diminished or in abeyance. The term “remission” is used when one cannot say with confidence that the disease has been cured.

REMUNERATION - Payment for participation in research.

RESEARCH - A systematic investigation (i.e., the gathering and analysis of information) designed to develop or contribute to generalizable knowledge [45 CFR 46.102 (d)].

RESEARCH INVESTIGATOR - In clinical trials, an individual who actually conducts an investigation [21 CFR 312.3]. Any interventions (e.g., drugs) involved in the study are administered to subjects under the immediate direction of the Research Investigator. (See also: Principal Research Investigator).

RESEARCH REVIEW COMMITTEE - Former name of The Institutional Review Board for The Lankenau Hospital and The Lankenau Medical Center.

GLOSSARY OF TERMS

RESPECT FOR PERSONS - An ethical principal discussed in the Belmont Report requiring that individual autonomy be respected and that person with diminished autonomy be protected.

RETROSPECTIVE STUDIES - Research conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records) or by obtaining information about past events elicited through interviews or surveys. Case control studies are an example of this type of research.

REVIEW OF RESEARCH - The concurrent oversight of research on a periodic basis by an IRB. In addition to the at least annual reviews mandated by the federal regulations, reviews may, if deemed appropriate, also be conducted on a continuous or periodic basis [45 CFR 46.109 (e)].

RISK - The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary from minimal to significant. Federal regulations define only “minimal risk”.

SECRETARY - A U.S. Cabinet Officer. In the context of DHHS-conducted or -supported research, refers to the Secretary of Health and Human Services.

SIGNIFICANT RISK DEVICE - An investigational medical device that presents a potential for serious risk to the health, safety, or welfare of the subject.

SINGLE-MASKED DESIGN - Typically, a study design in which the Research Investigator, but not the subject, knows the identity of the treatment assignment. Sometimes called “single-blind” design.

SITE VISIT - A visit by agency officials, representatives, or consultants to the location of a research activity to assess the adequacy of IRB protection of human subjects or the capability of personnel to conduct the research.

SPONSOR (OF A DRUG TRIAL) - A person or entity that initiates a clinical investigation of a drug - usually the drug manufacturer or research institution that developed the drug. The sponsor does not actually conduct the investigation, but rather distributes the test article to Research Investigators and physicians for clinical trials. The drug is administered or dispensed to or used involving, subjects under the immediate direction of a Research Investigator who is not also a sponsor. A clinical Research Investigator may, however, serve as a sponsor-Research Investigator. The sponsor assumes responsibility for investigating the new drug, including responsibility for obtaining FDA approval to conduct a trial and for reporting the results of the trial to the FDA.

SPONSOR-RESEARCH INVESTIGATOR - An individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual.

GLOSSARY OF TERMS

SURROGATE – the following individuals may be considered legally authorized representatives of the subject and capable of providing surrogate consent and/or surrogate HIPAA Authorization: (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 proxy 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 following order, (a) spouse, (b) natural or adoptive parent, (c) adult child, (d) adult brother or sister or (e) an adult individual with significant personal relationship with the subject to warrant their authority outside the currently accepted legal spousal relationship. (In situations as described in this subsection e, Investigator should document the reasons why such relationship is considered to be significant and analogous to a legal spousal relationship.)

SURVEYS - Studies designed to obtain information from a large number of respondents through written questionnaires, telephone interviews, door-to-door canvassing, or similar procedures.

TEST ARTICLE - Any drug (including a biological product for human use), medical device for human use, human food additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

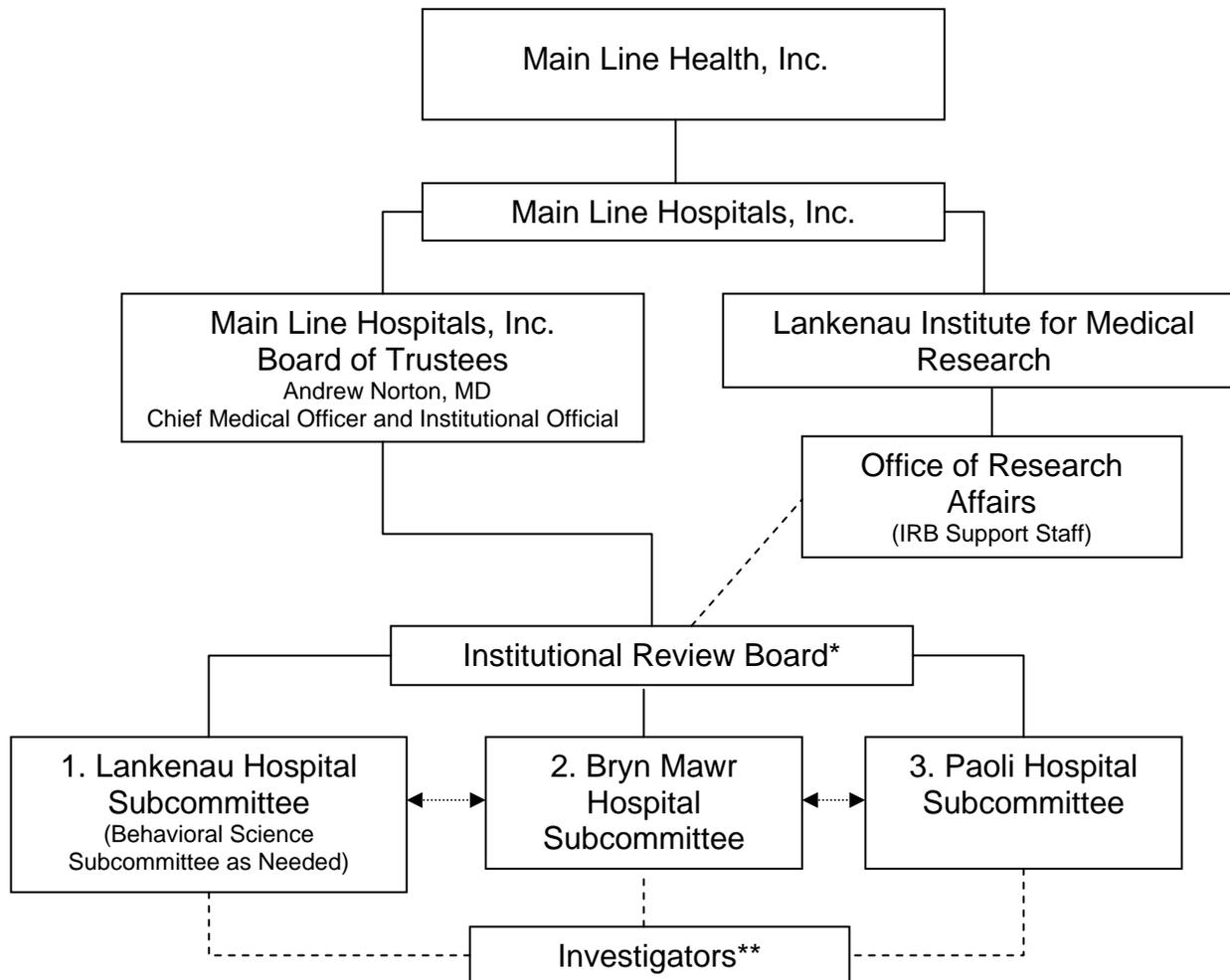
THERAPEUTIC INTENT - The research physician's intent to provide some benefit to improving a subject's condition (e.g., prolongation of life, shrinkage of tumor, or improved quality of life, even though cure or dramatic improvement cannot necessarily be effected). This term is sometimes associated with Phase I drug studies in which potentially toxic drugs are given to an individual with the hope of inducing some improvement in the patient's condition as well as assessing the safety and pharmacology of a drug.

THERAPY - Treatment intended and expected to alleviate a disease or disorder.

VIABLE INFANT - When referring to a delivered or expelled fetus, the term "viable infant" means likely to survive to the point of sustaining life independently, given the benefit of available medical therapy [45 CFR 46.203(d)]. This judgment is made by a physician.

VOLUNTARY - Free of coercion, duress, or undue inducement. Used in the research context to refer to a subject's decision to participate (or continue to participate) in a research activity.

Main Line Hospitals, Inc. Institutional Review Board Organizational Chart



- IRB is a subcommittee of the Main Line Hospitals (MLH) Board of Trustees.

- Through Main Line Health Institutional Official, the IRB reports directly to the MLH Board of Trustees.

- IRB has authority to make final determinations on the protections of human subjects in research, subject to authority of MLH Board of Trustees which may disapprove research but can not approve a study disapproved by the IRB.

- IRB is composed of 3 subcommittee units with some overlapping membership.
- Office of Research Affairs oversees all research activity which is under the jurisdiction of the IRB, and provides technical and administrative support to the IRB.

- Director of Office of Research Affairs reports to the Main Line, Inc. Institutional Official

*Bryn Mawr Rehabilitation Hospital (BMRH) and Riddle Memorial Hospital (RMH) are subsidiaries of Main Line Health, Inc. Any of the 3 subcommittees may review research conducted at BMRH and RMH.

** Investigators may be employees of the Main Line Health System or independent investigators.