LEGACY IRB

STANDARD OPERATING PROCEDURES
2014

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1. INTRODUCTION

The Institutional Review Board (IRB) is responsible for the review and approval of all research involving human subjects that utilize Legacy Health (LH) facilities, resources or patients. The IRB is a federally mandated board charged with protecting the rights and welfare of human research subjects recruited to participate in research activities and to ensure compliance with applicable LH policies and federal and state regulations. The IRB is responsible for reviewing, approving, and monitoring all research projects involving human subjects.

LH includes Legacy Emanuel Medical Center, Randall Children's Hospital at Legacy Emanuel, Legacy Good Samaritan Medical Center, Legacy Mt. Hood Medical Center, Legacy Meridian Park Hospital, Legacy Salmon Creek Medical Center, Legacy Research Institute, and all the Legacy clinics. At LH there are two IRBs, one that meets at Legacy Good Samaritan, and one that meets at Legacy Emanuel. Both IRBs can review research at any Legacy facility.

LH maintains a Federal Wide Assurance with the Department of Health and Human Services' Office for Human Research Protection (OHRP). That assurance (FWA 00001280) commits LH to comply with applicable federal regulations governing the conduct of all research involving human subjects and is reiterated at Legacy in administrative policy LH100.18.

OBJECTIVES
The objective of this SOP is to aid investigators and their staff in understanding their obligations and responsibilities in conducting human subjects research at LH.

SCOPE
This SOP applies to all personnel involved in the implementation and coordination of investigations involving human subjects at LH. Primary responsibility lies with the Principal Investigator/Co-investigator(s) and, when delegated by the investigator, research coordinators, nurses, and other appropriately experienced and trained personnel.

2. DEFINITIONS

Common Rule: The regulations governing IRBs for oversight of human research came into effect in 1981 following the 1975 revision of the Declaration of Helsinki and are encapsulated in the 1991 revision to the U.S. Department of Health and Human Services and is the baseline standard of ethics by which any government-funded research in the United States. At LH the Common Rule is covered by the both 45CFR46 (OHRP) and 21CFR56 (US Food and Drug Administration - FDA).

Clinical Research: Branch of medical science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment regimens intended for human use. These may be used for prevention, treatment, diagnosis or for relieving symptoms of a disease. **Clinical research** is research that directly involves a particular person or group of people, or that uses materials from humans, such as their behavior or samples of their tissue. A **clinical trial** is one type of clinical research that follows a pre-defined plan or protocol.

Human Subject: A living individual about whom an investigator conducting research obtains (l) data through intervention or interaction with the individual, or (2) identifiable private information.

Institutional Official: A position that is required to be the single point of responsibility for the oversight of research and the IRB functions. At Legacy Health the Institutional Official (IO) is appointed by the Chief Executive Officer (CEO) and has the title of Clinical Vice President of Research. The IO of Legacy Health has the legal authority to act and speak for the institution in regards to legal and contract matters relating to research with the federal government as well as all other sponsors of research. The IO appoints the members of the IRB and may veto any decision made by the IRB. In turn, the IO may not approve any activity disapproved by the IRB.

Institutional Review Board (IRB): A federally mandated committee charged with protecting the rights and welfare of human research subjects recruited to participate in research activities and to ensure compliance with applicable Legacy policies as well as state regulations and the Common Rule.

Interaction: Includes communication or interpersonal contact between investigator and subject.

Intervention: Includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes.

Principal Investigator (PI): At LH the authority to conduct a research study is granted by the IRB to a single individual, the PI, who in turn delegates authority to all other individuals who are involved including co-investigator, key personnel and other staff.

Private Information: Individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) that is gathered in the course of a research project and not publicly accessible information.

Protected Health Information (PHI): As defined by Health Insurance Portability and Accountability Act (HIPAA) any information that 1) is received by a health care provider, health plan or clearinghouse, 2) is transmitted electronically or maintained in any other form or medium (including oral), 3) relates to the provision of or payment for health care for a patient or to the past, present or future physical or mental health

condition of a patient, and 4) is individually identifiable. Information is presumed to be de-identified if all of the following identifiers have been removed or concealed:

a. patient name;
b. street address, zip code, city;
c. phone number;
d. fax number;
e. email address;
f. birth date, admission date, discharge date, date of death, all ages over 89;
g. social security number;
h. medical record number;
i. account number;
j. health plan beneficiary number;
k. certificate/license number;
l. vehicle ID number, license plate number;
m. device identifier number and serial number;
n. Web Universal Resource Locator number;
o. Internet Protocol (IP) address;
p. fingerprints, voice prints, other biometric identifier;
q. full face photographic images; or
r. any other unique identifying number, characteristic or code and any associated health information.

Registry: An activity that involves a central agent for the collection of clinical, laboratory, x-ray, pathological specimens and/or other data so organized that the data can be processed and made available for study.

Research: Defined by the Common Rule as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

3. IRB REVIEW PROCESS

Members: Per the Common Rule the membership of each IRB consists of at least five members, who are appointed by the IO. At a minimum, to assure diversity, the membership of the Board must include representatives from the following areas: 1.) scientific; 2.) non-scientific; and 3.) community. Board members are appointed as needed and serve at the discretion of the IO. Each IRB has a Chair and Vice-Chair who serve at the discretion of the IO. The members of the IRB must have expertise in the specific areas of review. At Legacy, each IRB has approximately 11 members.

Meetings: At LH there are two IRBs, one that meets at Good Sam and one at Emanuel. Both can review studies that are based at any Legacy facility. Meetings of each IRB are held once per month. The Chair may call an additional meeting if indicated. A majority plus one of the IRB constitutes a quorum, which includes at least one member whose primary concerns are in nonscientific areas.

Decisions of the Board: Decisions by the IRB are by majority vote of members. A member at the meeting having a significant conflicting interest (e.g. as principal investigator, co-investigator or coordinator) can not vote on that matter and must be absent from the room during the deliberation and voting. A member with a conflict of interest may be in attendance to answer questions related to the study.

Actions on Research Proposals: The IRB reviews research proposals submitted to it and shall periodically conduct ongoing or continuing review of approved research projects. Consideration will be given during the approval process by the IRB to determine the review frequency for the study.

Exempt from Review: The Common Rule identifies six categories of research that may be eligible for exemption from IRB review. The LH IRBs apply these six exemption categories only to protocols determined to be no more than minimal risk. If an investigator believes his or her research falls into one of these exemption categories, he or she must still submit a protocol to an IRB. Only an IRB can determine whether the research is exempt from review. The IRB has the right not to exempt a protocol and to require full review by the convened IRB or expedited review by an IRB member or IRB subcommittee, particularly if the research involves a sensitive population or sensitive topic.

Expedited Review: The Chairs or Vice-Chairs may review and approve minor amendments or studies that involve no more than minimal risk to the subject as specified in the Common Rule. If they are unable to approve those studies or amendments they must instead be referred to the full IRB for consideration. Continuing reviews of projects are conducted by full Board meetings unless they involve minimal risk or have not yet enrolled any subjects and then may receive expedited review. The Chairs or Vice-Chairs may delegate these reviews to any other member of the board that they deem qualified.

Administrative Amendments: The Research Regulatory Specialist is authorized to approve any administrative amendments, ie. those amendments that do not directly affect patient care.

Participation of Non-Members: Persons who are not members of the Board may attend the meetings with the consent of the Chair. If non-members are actively involved in a protocol being discussed, they must excuse themselves from the meeting prior to voting. The IRB may invite individuals with competence in special areas to assist in the review of complex issues that are beyond the expertise of the IRB. These individuals may not vote as part of the IRB.

Functions of the IRB: The IRB is tasked with ensuring the rights and safety of the research subject. Research projects should be reviewed in a manner so as to provide for the protection of the subject against undue or unnecessary invasion of privacy, disregard for human dignity, and physical, psychological or social harm. Decisions to approve research proposals is based on weighing the risks to the subject and comparing them to

the potential benefits to the subject plus the potential benefits to generalizable knowledge. Once the IRB has determined that such risks and benefits are relatively equal, then they must ensure that subjects are presented with appropriate information during a consent process that will allow them to make an informed decision concerning participation.

Responsibilities of the Chair: The Chair, and when appropriate the Vice-Chair, are responsible for:

1. Conducting the IRB meeting
2. Review investigational treatments in emergency situations
3. Expedited initial review of minimal risk studies including research registries
4. Expedited review of protocol modifications that do not increase the risk to the subject
5. Determine exemption status for activities submitted for review including retrospective chart reviews and quality registries
6. Review on-site new/unexpected serious adverse events
7. Liaison to the Principal Investigators as needed
8. Liaison to Medical Staff committees/individuals as needed
9. Suspend studies due to unexpected serious hazards to research subjects
10. Suspend studies due to investigator non-compliance and/or protocol violations that are serious in nature and/or represent a pattern of misconduct

Review Process: A primary and secondary reviewer system is utilized for the review of proposals. These reviewers will receive at a minimum the IRB Questionnaire, the full protocol, the consent form(s) and the CV of the principal investigator. All other members will receive the IRB Questionnaire and the consent(s). However, all research protocols will be made available for review by any member of the IRB, and any member of the board may, upon request, review the full protocol.

IRB Decisions: The IRB has the sole authority to approve, modify, or disapprove research activities covered by these policies. The IO may veto any decisions made by the IRB but may not overrule disapprovals.

The IRB will assess serious adverse events, suspected or alleged protocol violations, subject complaints, or violations of governmental regulations or institutional policies. Such incidents or allegations may be referred to the IO for further investigation and action, as appropriate. The IRBs have the authority to suspend or terminate approval of research that is not conducted in accordance with the IRB's requirements or that has been associated with serious harm to subjects. The Chair or the Chair's designee shall be authorized to take immediate action to suspend IRB approval of research for any serious noncompliance or unanticipated problems involving risks to subjects or others. A subcommittee may be appointed by the Chair or Chair's designee to assess suspected or alleged violations or complaints. The subcommittee shall report to the IRB and IO and may recommend actions to take on research project(s). Any suspension or termination of approval will include reasons for the IRB's actions and will be reported promptly to the investigator, the IO and federal officials as required.

No external body or official may override IRB disapprovals, nor apply undue pressure on the board to reverse a decision. The board may, upon the request of an investigator or on its own initiative, reconsider any proposal and reverse its own determination.

Continuing Review: The IRB will conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. It shall have authority to observe or have a third party observe the consent process and the performance of the research. Although certain types of continuing review may be conducted under the expedited review procedure, (e.g., minimal risk studies, studies in which no subjects have been enrolled or research which is permanently closed to subject enrollment), otherwise continuing reviews must be conducted by the full IRB. Investigators are initially requested to submit a continuing review two months prior to the review date and given two more reminders as the deadline approaches. Studies that do not comply with requests for review in a timely manner are suspended and instructed on how to reapply.

Duration of IRB Oversight: Continuing review by the IRB is required as long as investigators are either interacting or intervening with subjects for research purposes, or accessing identifiable private information and PHI for research purposes. For multi-site research, it is acceptable to close the study if investigators are neither interacting with nor accessing subject information, as outlined above.

Prospective Review: The IRB requires that any changes in research activity be reviewed and approved prior to implementing those changes, except where necessary to eliminate apparent immediate hazards to the human subjects. These changes will be reviewed and approved via an amendment form. Minor changes may be reviewed by an expedited review procedure; however, substantive changes must be reviewed by the full board at a convened meeting. New primary objectives or significant changes in the statistical design constitute a new study and are not justified as amendments.

Record Retention: The IRB will maintain, for at least three years after the completion of a study, records of research protocol reviews and minutes of meetings, including records of attendance and IRB deliberations. Deliberations and decisions of the IRB associated with research activities shall be considered confidential, except insofar as the dissemination of information regarding deliberations, decisions, recommendations, etc. to appropriate institutional officials as required by law and/or policies of the IRB. Failure to adhere to this provision may be cause for removal of a member from the IRB.

4. CONFLICT OF INTEREST

IRB Members: No IRB member can 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. For the Legacy IRB, conflicts of interest include those situations where individuals are involved in the conduct of the study as principal investigator or paid consultant. Another conflict is having financial relations with the sponsor of the

study. Professional association and administrative duties do not necessarily pose a conflict of interest as long as those relationships are known to the committee. For instance, pharmacy staff who are IRB members may review drug studies. Similarly, administrators may review studies that affect their departments and physicians may be involved in reviewing studies conducted by their office partners if they are not named co-investigators. In each instance those relationships will be disclosed prior to the review and a majority of the IRB will determine whether the potential conflict should prohibit the member from participation in review and abstaining from voting.

PI and Key Personnel: Principal Investigators and Key Personnel at Legacy will report any significant financial conflict of interest meaning anything of monetary value or in kind including but not limited to salary or other payments for services (e.g. consulting fees or honoraria), equity interests (e.g. stocks options or other ownership interests) and intellectual property rights that exceed $5,000 per annum if salary, fees or other continuing payments represent more than a 5 % ownership for any one enterprise.

Investigators at Legacy will also report any financial benefits made available in connection with the conduct of a study that are in addition to the ordinary compensation for services, beyond customary and reasonable fees, including incentive pay, rewards for early recruitment, or bonuses for reaching enrollment goals. In the event a conflict of interest is revealed, the Legacy IRB is tasked with determining what action should be taken to manage that conflict. These actions may include but are not limited to:

1. public disclosure of the conflict through inclusion in the consent form
2. monitoring of the research project by independent reviewers
3. modification of the research plan
4. disqualification of the investigator from participating in all or a portion of any sponsored research including recruiting subjects and analysis of data
5. divestiture of an investigator of any financial interest in any research sponsor

In addition, Principal Investigator and Key Personnel whose research is funded by the Public Health Service (NIH, AHRQ, CDC, FDA and others) are required to make yearly disclosures and to have undergone COI training through the CITI program.

5. PROPOSAL SUBMISSION

The following documents are required for review:

1. Initial Review Questionnaire with signatures by the Principal Investigator and, when appropriate, signatures for Administrative Review.
2. Protocol.
3. For drug studies – Investigator's Brochure, three copies.
4. For device studies – Pre-clinical data or supporting literature.
5. Consent form with LH specific language.
6. Principal Investigator's CV.

6. IRB COMMUNICATION

The processes and decisions of the Legacy IRB must be communicated in a clear and direct manner with Principal Investigators, Sponsors and Legacy Administration. In addition, those decisions made by the Chair or Vice-Chair, for instance expedited approvals, approval of retrospective chart reviews and adverse event reporting, must be communicated to the IRB.

Communication with Principal Investigators

1. Initial Contact – Principal Investigators either access the IRB application packet on the Legacy Internet or contact the IRB office to request copies of the IRB Questionnaire and Consent form template. They are also given two instructional documents entitled "Read Me – Sponsors" and "Read Me – Investigators".
2. Upon receipt of an IRB application the Principal Investigator is notified by phone or e-mail that the proper documents have been received. The PI is then notified of the meeting date and invited to attend the meeting.
3. The presence of the PI at the meeting is not mandatory but is encouraged in order to provide the PI the opportunity to answer questions. The PI is asked to leave the room during the deliberation and voting.
4. The outcome of the IRB meeting is communicated to the PI through a letter which is sometimes e-mailed in order to facilitate a timely response. That letter is written by the IRB Coordinator or the IRB Chair and communicates the circumstances of approval, disapproval or tabling of the proposal. Such communication is sent to the PI as well as their study coordinator.
5. In most cases IRB correspondence is drafted by the IRB Coordinator. IRB members will be kept informed via e-mail of the text of those letters in those instances where complex changes in the consent form are requested or when clarification of the protocol or other contingencies are requested.
6. In some instances the IRB may decide to meet with the PI outside of a meeting in order to communicate decisions in a less formal manner. Those meetings are organized by the IRB Coordinator and may involve the Chair, Vice-Chair or primary and secondary reviewers of the proposal.
7. Continuing Review – Continuing Review must be conducted at least every twelve months and in some cases more often, depending upon the circumstances of the initial review. The IRB requests that the PI update the committee on the progress of the investigation to include whether all serious adverse events have been reported, whether the study is being conducted according to the approved protocol. In addition, a 150 word summary is requested that documents progress to date and whether any publications have resulted. The IRB may request a continuing review at any time interval or per number of patients and may request any amount of information regarding the study. Ten months after the initial approval of a study the Principal Investigator receives a document entitled "Continuing Review Questionnaire". If the paperwork is not filed with the IRB in a timely manner the PI will receive two more notices. Non-compliance will result in suspension of the study.

Communication with Sponsors
Sponsors may include drug and device companies, federal agencies and foundations as well as other sources of funding. Generally the IRB does not communicate directly with sponsors and prefers to communicate only through the PI. Exceptions are made for those instances in which the investigator is unable to provide information requested by the IRB.

Legacy Administration

1. E-mail Minutes – The IRB minutes and agenda are distributed to both committees and a range of interested others within LH including Pharmacy, Purchasing, Medical Staff Services, Site Administrators, Senior Administration and several senior members of the Legacy medical staff.
2. Institutional Official – The IO receives the minutes for each meeting and is responsible for providing final signatory approval for each study.
3. E-News – The Research Department issues an e-mail newsletter to 6000 out of 8000 employees of LH. This newsletter is also sent out as a pdf file so that it can be printed and passed around or posted for those employees who do not have e-mail access.

Information routinely reported to the IRB: The IRB will be kept informed of expedited approval and exemption determinations as well as deferral arrangements with external or central IRBs, as well as emergency use and retrospective chart reviews through a section of the agenda entitled "Information". Such "Information" will be distributed in the IRB review packets and will contain paperwork that describes what items did not reach full board review. Any member of the IRB can request more details about such items and can initiate discussion as to whether such items should be reviewed by the full board even in those circumstances where the Chair or Vice-Chair has already approved of the expedited study activity.

7. INFORMED CONSENT

Informed consent is one of the primary requirements that are designed to ensure the ethical conduct of research involving human subjects. It reflects the basic principles of respect for persons, voluntary participation and individual autonomy. Informed consent is an on-going process, not a signed document or a legally binding agreement. Informed consent should be obtained under circumstances which allow the research subject the opportunity to adequately assess the risks and benefits. The Principal Investigator or their designee is responsible for conducting the consent process. The IRB is responsible for the content of the consent form which is used to guide that process. The consent form is signed to indicate when the initial consent process occurred. Participation in research is always voluntary and subjects may with draw at any time. The research subject will receive a copy of the consent form, not necessarily the signed copy, and it should be used as an information sheet that the subject can refer to prior to volunteering for the research study and as a reference document during the conduct of the study.

General Requirements

1. A statement that the study involves research;
2. An explanation of the purpose of the research;
3. The expected duration of the procedures to be followed;
4. A description of the procedures to be followed;
5. Identification of any procedures which are experimental;
6. A description of any reasonably foreseeable risks or discomforts to the subject (includes ineffective treatment, if any);
7. A description of any benefits to the subject or to others reasonably expected from the research;
8. A disclosure of specific appropriate alternative procedures or courses of treatment, if any, advantageous to the subject;
9. A statement informing the subjects that their medical records may be examined by the sponsor and, if so, the extent to which those records will be kept confidential;
10. A statement that notes the possibility of the FDA inspecting records;
11. An explanation as to whether any compensation is available if injury occurs (more than minimal risk studies);
12. An explanation as to whether any medical treatments are available if injury occurs (more than minimal risk studies);
13. An explanation of whom to contact for answers to pertinent questions: About the research; About research subject's rights; Whom to contact in the event of research-related injury;
14. A statement that participation is voluntary;
15. A statement that refusal to participate will involve no penalty or loss of benefits;
16. A statement that the subject may discontinue participation at any time without penalty or loss of benefits;
17. Liability Statement – specifying in the case of a serious adverse event the limits of coverage by LH and/or the sponsor;
18. A statement that the subject will receive a copy of the consent form;
19. A statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable;
20. A statement of anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
21. Any additional costs to the subject that may result from participation in the research;
22. The consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject;
23. 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;
24. The approximate number of subjects (and sites) involved in the study;
25. A description of the PHI to be used or disclosed;
26. Names of the persons or class of persons who will use PHI or to whom it will be disclosed;
27. A description of the purpose of the requested use or disclosure;
28. Authorization expiration date or expiration event;

29. Right to revoke and how to do so;
30. Whether treatment or participation can be conditioned on Authorization and the consequences of refusing to sign;
31. Risk that PHI will be re-disclosed or statement that the Privacy Rule may no longer protect PHI disclosed to the recipient.

Consent Form Language

The consent form must be written in approximately 8th grade language (like a newspaper). The first time a technical or scientific word is used it must be defined. The first time an abbreviation is used it must be spelled out. Consent forms should be written in the third person (you rather than I). There must be no coercive language such as phrases like "You understand that your participation...". Ideally the consent form should be written in the active voice rather than passive; an easy rule to follow is delete all qualifying statements and use as few compound sentences and conjunctions as possible.

Consent Form Stamp

It has been the practice of the LH IRB to have the IRB Chair or IRB Coordinator stamp, sign and date the first page of approved consent forms. That is done to signify the approved text and is meant to be retained by the investigator in the regulatory binder. In some cases investigators have used a copy of that stamped and signed consent form to present to research subjects. This practice should be discouraged because it is potentially coercive, giving the impression that the research study is safe because it has received the stamped approval of the LH IRB. In addition, generally there is no explanation in the consent form as to the role and function of the IRB. Text providing such an explanation would be superfluous to the document and would add no additional information for the subject to make their informed decision whether to participate in the trial. For that reason, all stamped Consent Forms should only be maintained in the regulatory binder and those given to subjects should not have the stamp and signature affixed. In order to make it clear which copy of the consent form is approved, there should be a revision date or version number in the footer in 8 point font that corresponds to the most recent stamped form.

Consent Form Signatures

The consent document is a written summary of the information that should be provided to the subject. Many clinical investigators use the consent document as a guide for a verbal explanation of the study. The subject's signature provides documentation of agreement to participate in the study, but is only part of the consent process.

The following signatures **must** be affixed to the consent form and dated:

- signature of research subject
- signature of principal investigator or their designee who is conducting the consent session

The following signatures **may** be affixed to the consent form and dated:

-signature of witness (someone not involved in the study, the witness must be present during the entire consent process)
-signature of parent or legal guardian
-signature of next of kin (if research subject is not cognitively competent to consent); next of kin is defined as being spouses, parents, children (including adopted children), brothers, sisters and spouses of brothers and sisters, and any individual related by blood or affinity whose close association with the subject is equivalent to a family relationship.

Surrogate Consent

If a prospective subject cannot consent on his/her own behalf, federal regulations permit researchers to obtain consent from a legally-authorized representative. In order for researchers to obtain consent from a subject's legally-authorized representative, the IRB must approve the use of surrogate consent. Individuals whose medical condition may render them temporarily unable to provide informed consent as a consequence of severe pain, confusion, or impaired consciousness due to events such as life-threatening illness or trauma, and individuals who have cognitive impairments such as intellectual disabilities, dementia, or psychosis that are enduring or that may worsen with time. Those individuals who may grant surrogate consent include:

- a person's agent designated by an advance health care directive,
- a conservator or guardian of the person having the authority to make health care decisions for the person
- spouse of the person
- domestic partner of the person
- adult son or daughter of the person
- custodial parent of the person.
- any adult brother or sister of the person
- any adult grandchild of the person
- an available adult relative with the closest degree of kinship to the person.

In the event that surrogate consent is sought, the PI or their staff will document the circumstances under which it was obtained (or not) and the relationship of the surrogate to the subject.

Date and Time of Consent

Each signature line must include a place to note the date but the time of consent is not routinely required. The purpose of writing down the time of consent may be requested by the IRB, the investigator or the sponsor. The purpose of noting the time of consent is to provide an indicator that consent was obtained in a manner that allowed the subject sufficient time to consider the risks, benefits and alternatives.

Subject Initials on Consent Forms

In some instances sponsors and/or investigators include a footer on each page of Consent Forms for research subjects to initial. Although there is no regulatory guidance requiring subject initials on each page, it is the practice of the LH IRB to delete those footers as they imply that the Consent Form is a legal contract rather than an information sheet. For that

reason, all Consent Forms approved by the LH IRB will not contain footers on each page for the subject to initial.

Consent Obtained over the Telephone for Treatment Trials
A consent session conducted over the telephone does not satisfy the regulatory requirement for treatment trials for a face to face consent process. However, in some those studies where the patient is not conscious or cognitively impaired, or for any other reason unable to provide informed consent, it is acceptable to send the informed consent document to the legal authorized representative by FAX and conduct the consent interview by telephone when the representative can read the consent as it is discussed. If the legally authorized representative agrees, they can sign the consent and return the signed document to the clinical investigator by FAX prior to initiation of the experimental treatment.

Consent Obtained over the Telephone for Minimal Risk Studies
Studies which involve surveys, interviews or other minimal risk studies, may, in some instances, qualify for a waiver of the usual requirement of written signed consent. In those instances, a script will be submitted by the PI to the IRB and approved in place of a consent form.

Waiver of Elements of Informed Consent
The IRB may approve a consent procedure which does not include, or which alters some or all of the elements of prospective informed consent if the research could not be practicably carried out without the waiver or alteration, the research involves no more than minimal risk, and the waiver or alteration would not adversely affect the rights and welfare of the subjects. For instance, anonymous surveys may be granted a waiver of informed consent as participation in the survey would indicate consent, and because no subject identifiers would be maintain, the main risk being breach of confidentiality would be eliminated.

Non-English Speaking Subjects
If a non-English consent form is needed, the investigator should have the final IRB approved English version of the study consent translated by the sponsor or a translation service. Then the translated consent form must be submitted to the IRB with a letter certifying that it is equivalent. The certification letter may come from the translating service or from LH's translation service. Informed consent of non-English speaking subjects must be conducted with a translated consent form and utilizing the services of an employee of Legacy's translation service.

In those instances where the investigator feels that it is in the non-English speaking patient's best interest to receive an experimental treatment, then they should use their clinical judgment, treat the patient and then immediately report the "emergency use" to the IRB. Such patients are not research subjects and any data gathered during their clinical course cannot be shared with the sponsor or used for any research purposes or application to the FDA.

Assent of Children

Assent is defined as a child's affirmative agreement to participate in research. Although consent is a legal requirement, assent has no legal basis and is instead an ethical concept. Children should only be invited to consider assenting in research studies in which their parents and physician will honor their dissent. In those instances, two consent documents are developed; one for the parent(s) to sign, and one for the child. The assent form must outline the study in simplified form, explain the procedures involved and stress that participation is voluntary. Assent need not be positively expressed and so the investigator must accept the responsibility of recognizing passive dissent. Generally assent is sought from children age 9 and above. The circumstances under which adults honor dissent are based on age and the severity of the condition. For instance, a child's protestation against an injection of an experimental drug intended to treat a life threatening condition would not be honored. The objections of a child to a blood draw for genetic analysis looking for a predisposition to a disease for which there is no treatment would be given greater weight.

Communicating Consent Form Changes to Study Subjects

The LH IRB does not encourage or condone "re-consenting" subjects. In those instances subjects are presented with a consent form that is largely similar to the one that they signed upon entering the trial with changes in the risk or schedule sections. Instead the LH IRB insists that PIs and sponsors communicate those changes in a more direct manner.

Changes in the consent form that occur after a research subject has already consented to be in the study that need to be brought to the attention of the research subject are generally of two types:

1. changes in the schedule of events;
2. update on risk assessment.

Notification of schedule changes can be done with a simple letter or memo to the subject along with a verbal reminder at their next clinic visit.

Updates on risk assessment should be communicated immediately through a phone call or letter to the subject or both, and then at the next clinic visit that information should be presented in the form of a consent addendum. The consent addendum should be limited to just the new risks that have emerged during the course of the study. A signature of the participant and the researcher on the consent addendum is required to document that the research subject has been made aware of the updated risk assessment. Consent addendums, letters and memos to subjects, and phone scripts communicating such changes must be reviewed and approved by the IRB.

Use of Screening Consent Form

In those instances where patients go through extensive screening processes prior to enrollment, a screening consent form can be used. That consent form will describe the main study briefly and concentrate on the purpose, procedures and risks of the screening processes. A screening consent form is intended for those studies where it is anticipated that

there will be high number of screen failures and/or involve procedures that pose a risk to the subject. Screening consent forms must be reviewed and approved by the IRB.

Receptionist Scripts
The first contact study subjects make is often with a receptionist who follows a script to determine basic eligibility. In some cases personal and sensitive information is gathered about the individual. The IRB should assure that the procedures adequately protect the rights and welfare of the research subject. Issues for IRB review of scripts include: what happens to personal information solicited during the phone conversation? Are names collected and then used for another study? Receptionist scripts are considered part of the consent process and must be reviewed and approved by the IRB.

Executive Summary
For those studies which are very complicated or are presented to the potential subject or their LAR in an emergency or difficult medical circumstance, the executive summary is presented to help the subject or LAR to help decide whether they want to consider participation in the study. The executive summary is a one page document that is not designed to be a substitute for a consent form but serves as an introduction to the study. It must contain a brief summary of the purpose of the study, the activities of participation and the risks.

8. ADVERTISING

The recruitment of research subjects for clinical trials is considered part of the informed consent process. All advertisements that may be seen or heard by a potential research subject must be approved by the IRB prior to its use**.** IRB review of advertising is necessary to ensure that the information is not misleading to potential subjects.

Any communication that is seen or heard by prospective subjects to solicit their participation in a study includes but is not limited to newspapers, TV, radio, bulletin boards, posters, letters and flyers.

Any communication intended to be seen or heard by health professionals such as “dear doctor” letters and doctor-to-doctor communication (even when soliciting for study subjects), news stories, and publicity intended for audiences such as financial page advertisements directed toward prospective investors are not considered to advertising and are viewed as professional communication and so do not need to be reviewed by the IRB.

The FDA suggests but does not require that the following items should be contained in an advertisement:

1. the name and address of the clinical investigator and/or research facility
2. the condition under study and/or the purpose of the research
3. the criteria that will be used to determine eligibility
4. a brief list of participation benefits, if any
5. the time or other commitment required of the subjects
6. the location of the research and the person or office to contact for

further information

An advertisement should not contain claims either explicitly or implicitly that the drug or device is safe or effective or that the test article is known to be equivalent or superior to any other drug or device. Advertising should not use terms such as "new treatment", "new medication" or "new drug". Similarly, phrases such as "receive new treatments" or "relieves symptoms" should not be used as they may lead study subjects to believe that they will be receiving newly improved products of proven worth.

9. HIPAA PRIVACY and SECURITY RULES

The Health Insurance Portability and Accountability Act of 1996 contained several components that guide the use of PHI in Research.

HIPPA Privacy
The HIPAA Privacy Rule went into effect in 2003 and contained special provisions about how patient information can be used in research.

1. General Rule. No research involving uses or disclosures of a subject's PHI may be conducted unless (a) an authorization for use or disclosure of such information is obtained from the subject, (b) a waiver of authorization has been approved by an IRB) (or a Privacy Board, as applicable), (c) the health information has been de-identified, (d) the health information is used or disclosed in a limited data set in accordance with a data use agreement, or (e) one of the exceptions listed in Part 2 below applies.

2. Exceptions. The following circumstances shall be exceptions to the Privacy Rule requirements of this policy:

    a A subject's PHI may be disclosed to a person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity, including but not limited to: (i) collecting or reporting adverse events, product defects or problems, or biological product deviations, (ii) to track FDA-regulated products, (iii) to enable product recalls, repairs, replacement or look back activities, or (iv) to conduct post marketing surveillance.

    b Protected health information may be used by or disclosed to a researcher as necessary to prepare a research protocol or for similar purposes preparatory to research provided the researcher represents to LH that: (i) the use or disclosure is sought solely for such purposes, (ii) no protected health information will be removed from LH's premises by the researcher in the course of the review, and (iii) the protected health information for which use or access is sought is necessary for the research purposes.

c Protected health information may be used by or disclosed to a researcher for research on decedents provided the researcher: (i) represents to LH that the use or disclosure is sought solely for research on the protected health information of decedents, (ii) provides to LH, upon request, documentation of the death of the research subject, and (iii) represents to LH that the protected health information is necessary for the research.

HIPAA Security

The HIPAA Security Rule went into effect in 2005 and contain special provisions about how PHI is managed within electronic records systems. Security is not a one-time project but rather an on-going dynamic process that will create new challenges as technology changes.

The Security Rule sets the standards for ensuring that those who should have access to electronic PHI will actually have access with appropriate safeguards.

When data is gathered using electronic devices the following safeguards must be taken:

- A current Business Associate and/or Confidentiality Agreement is in place for non-Legacy Health entities
- All personnel accessing the records are named
- Access to records limited to the named individuals by way of encryption and/or passwords
- Records transmitted over an open network or stored on a portable medium such as CD/DVD-ROM, laptop, USB drive is encrypted
- Access to the records logged for accountability purposes
- Review of records conducted in a physically secure environment
- Records will only be available in a "read-only" format and will not be duplicated from the original medium of conveyance
- Access to electronic records will "screen lock" after 15 minutes of idle time
- When records are no longer necessary, they will be destroyed or de-identified in a secure manner such that they are not recoverable

In order to assure that the Security Rule is followed the following actions are necessary:

- All medical records are abstracted manually and de-identified when stored on a personal laptop or other computer
- If records are stored on a laptop, CD/DVD or thumb drive; an assurance is provided that the laptop and any removable media are encrypted.
- Access to records will only occur in a physically secure environment, (ie. hospital, office, home office, etc). Access to records restricted only to authorized personnel by means of encryption and password protection where appropriate. Laptop shall automatically "lock" after 15 minutes of inactivity. A strong password will be used of at least 8 characters in length combining letters, numbers and symbols.
- If records are shared with a third party; confidentiality agreement will be obtained from with the third party and encrypt records copied to removable media (i.e. CD/DVDs, thumb drives, other).

- If less than 50 records are utilized for this project, each medical record logged that it was used for research purposes. When records are no longer necessary, they will be securely destroyed or de-identified. When named personnel are removed from project their access to the records will be blocked.
- In those instances where Legacy computers will not be used the Principal Investigator must contact Information Security to assure that appropriate protections are understood and in place.

Retrospective Chart Review

Retrospective review of medical records for research purposes requires the official request for waiver of patient authorization. Such a waiver is allowable if the research could not be practicably done without the waiver, the use or disclosure of PHI involves no more than minimal risk to the privacy of the patient, and there is an adequate plan to protect the identifiers from improper use or disclosure. In addition there needs to be a plan to destroy the identifiers at the earliest possible opportunity consistent with the research and an assurance that the PHI will not be reused or disclosed to any other person.

Retrospective review of medical records must involve only data that existed prior to the request and there must be no intent to contact patients. Applications for retrospective chart review must include the following documents:

A. A letter of intent explaining the purpose of the chart review including an assurance of confidentiality. That letter should contain a brief description of the study, specifying the number of charts to be reviewed and the time period when the patients received clinical care. The PI must provide an assurance that they are collecting the minimum necessary information to accomplish the task.

B. A data collection sheet must accompany the application. If there is any PHI that could identify the patient then the investigator must first justify gathering that information and then submit a plan as to how and when the PHI would be de-identified or the data set destroyed

10. DRUG STUDIES

A drug is any chemical compound that may be use on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation or prevention of a disease or other abnormal condition.

Investigational New Drug (IND)

The FDA's IND program is the means by which a pharmaceutical company is allowed to conduct safety and efficacy studies of drugs. Chemical entities studied under INDs include new molecular compounds, compounds that are similar to those already on the market and in some cases drugs that have previously been approved but are seeking approval for treatment of other conditions. An IND is required for a clinical study if it is intended to support a new indication, a change in the approved route of administration or dosage level, a change in the approved patient population or a significant change in the promotion of an approved drug. For IND studies the IRB receives a protocol and an Investigator's Brochure (IB) that outlines the known risks which are then reflected in the consent form.

The IB may contain data from previous human studies or animal studies, as well as chemical and manufacturing information.

Off-Label Use

The FDA regulates the drug approval process. Once a drug is on the market its use is determined by the clinical judgment of the physician. If a drug is used for an indication that is not approved by the FDA then it is called an off-label use. In some cases investigators may wish to study these off-label uses without the support of sponsors. In those instances they are required to submit the same documents as if they were conducting an IND. Often the Physician's Desk Reference pages and the package insert can substitute for the investigator's brochure. In addition, journal articles may be used to support risk assessments. Studies involving off-label use of a drug require an IND in those instances when the data from the study will be used to support a new marketing indication. The IRB may require any off-label use study to obtain an IND if there is any uncertainty as to who the data from the study will be used or if there are unusual safety concerns.

Open Label, Parallel Track, Treatment IND and Orphan Drugs

Open label studies are those carried out to obtain additional safety data and require full board IRB review. They are typically used when the comparison trial has ended and treatment is continued so that subjects may continue to receive the benefits of the investigational drug. Parallel track studies are open label studies that are conducted while other comparison studies are still under way. Parallel track studies are provided when the FDA is relatively certain that the drug provides a benefit. Treatment IND is for those conditions which are serious and life-threatening for which no approved treatment is available. A treatment IND may be granted by the FDA after enough evidence is gathered to indicate that the drug "may be effective". Treatment INDs differ from Emergency Use in that they are generally long term treatments of chronic conditions. An orphan drug is a pharmaceutical agent that has been developed specifically to treat a rare medical condition, the condition itself being referred to as an orphan disease. .

Biologics, Vaccines, Combination Products, Dietary Supplements and Botanicals

The Legacy IRB reviews medical products that are neither drug or device and sometimes products that combine both. Biologics include blood, vaccines and tissue. Dietary supplements and botanicals are created from plants, minerals and other natural sources. Combination products that involve both a drug and device include such items as drug-eluting stents and human demineralized bone matrix. In all cases, IRB review is same as an IND study. Biologics and combination products are regulated by the FDA just like drugs and devices. Dietary supplements and botanicals may be marketed without FDA trials that prove their safety and efficacy but in some cases investigators and sponsor may conduct clinical trials with these items. The difficulty of reviewing such studies commonly relates to the lack of pre-clinical data and lack of consistency in the manufacturing process.

11. MEDICAL DEVICE STUDIES

A medical device is defined as any health care product that does not achieve its primary intended purpose by chemical action. The FDA began regulating devices in 1976 and has developed a system that accommodates rapidly evolving technologies.

Today there are two major roads to market: Premarket Approval (PMA) which involves human clinical trials, and 510(k) which involves establishing "substantial equivalence" with an already marketed device or a device that was grandfathered into the FDA prior to 1976. Typically, each year approximately 200 new medical devices are approved through the PMA process while 2000 are approved each year by the 510(k) route.

Investigational Device Exemption (IDE)
The manufacturer must establish the safety and effectiveness of the device by conducting clinical trials. Those clinical trials are intended for devices whose malfunction or misapplication poses a serious risk to the patient or devices that are intended to have substantial importance in diagnosing, curing or preventing impairment. In order to conduct the clinical trials, the manufacturer must be granted an IDE from the FDA that includes a detailed protocol and an Investigator's Brochure that documents the materials testing, bio-compatibility testing and pre-clinical animal studies.

510(k)
The other major approval process, the 510(k), is used when a manufacturer can prove that a new device is "substantially equivalent" to a similar device that is already marketed. 510(k) devices generally involve minor advances in technology and most often there are no clinical trials required. For that reason the FDA does not allow manufacturers to state that 510(k) devices are "FDA approved" but instead they have been "cleared for marketing". In some cases the 510(k) approval is contingent upon the conduct of a short study. Such studies generally concentrate on safety monitoring while the efficacy of the device is generally a secondary concern. In other instances, the manufacturer may want to conduct small studies to ensure that the devices are safe.

Off-Label Use of Devices
The FDA regulates the device approval process. Once a device is on the market its use is determined by the clinical judgment of the physician. In some cases investigators may wish to study these off-label uses without the support of sponsors. In those instances they are required to submit the same documents as if they were conducting an IDE.

Non-Significant Risk (NSR) Devices
For some medical devices the manufacturer does not need to negotiate an IDE to conduct clinical trials. In those instances the IRB must determine whether the device poses a "Non-Significant Risk" to the patient.

NSR determinations are based on proposed use of the device and not the device alone. These determinations are made on a case by case basis to determine the following:

1. the device implanted is intended to be used in an on-going manner

2. the device is designed to be life sustaining
3. the device is of substantial importance in diagnosing, curing, mitigating, or treating disease
4. the device failure result in injury
5. safeguards are in place to reduce the potential for injury

If the IRB determines that the device poses a significant risk, then the manufacturer must file for an IDE with the FDA and conduct its study under an IDE even if other institutions have judged the device to be NSR.

Humanitarian Use Device (HUD)
The HUD program was established in 1990 with passage of the Safe Medical Devices Act and creates an alternative pathway for obtaining market approval for medical devices that may help people with rare diseases or conditions. A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year (21 CFR 814.3(n)). An HUD is essentially an orphan device for which there is evidence of safety and probable benefit, and which can only be used in facilities where an Institutional Review Board (IRB) provides oversight.

Initial Review
Except in the case of emergency use, the Legacy IRB must review and approve each HUD before use at LH facilities. These reviews may be conducted concurrently. The initial review of an HUD will occur at a convened meeting and will include the following: the HDE approval order, a description of the device, the product labeling, instructions for use, a summary of probable benefit, and a manufacturer-supplied patient information pamphlet.

Consent Requirements
The LH IRB has waived the requirement for a consent form and instead requests that the physician provide the patient with the manufacturer-supplied patient information pamphlet and a document entitled "Humanitarian Device: Information for Approving use at Legacy Health". In addition, the patient will sign the surgery consent form as appropriate.

IRB Oversight
As part of its oversight responsibilities the Legacy IRB gathers a copy of the Operative Report and Discharge Summary for each case completed. If patients experience a serious adverse event due to the device a report must be submitted to the IRB by the treating physician within five working days.

Continuing Review
The LH IRB may use an expedited review procedure for the annual continuing review. As part of this review, the Chair or designee should consider any new information that

could alter the risk/benefit ratio as well as the Medical Device Reporting reports submitted to the FDA by the manufacturer.

Off-label Use of a HUD
If the LH IRB has reviewed and approved the use of a HUD, a physician may use the HUD for any indication if s/he determines that there is no alternative device for the patient's condition. That off-label use needs to be approved by the IRB with supporting literature, weighing risks versus benefits, and an appropriate consent form. The physician must obtain informed consent from the subject and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient.

Emergency use of a HUD
If a physician in an emergency situation determines that IRB approval for the use of a HUD cannot be obtained in time to prevent serious harm or death to a patient, an HUD may be used without prior IRB approval. That use must be reported to the IRB within five working days.

12. EMERGENCY USES OF INVESTIGATIONAL AGENTS

The FDA regulates the development of drugs, devices and biologicals for the treatment of disease but does not regulate physician practice. Physicians may treat patients with investigational agents outside of a clinical trial in emergency circumstances which include "emergency use", "emergency use IND", "compassionate use", "single patient IND", "treatment IND", AND "Group C Protocols"

Physicians should be aware that the FDA expects them to exercise reasonable foresight with respect to potential emergencies and to make appropriate arrangements under the various procedures enough in advance to avoid creating a situation in which such arrangements are impracticable.

Emergency Use
An **emergency** is defined as a **life-threatening** or **severely debilitating** situation in a single patient for which is no standard acceptable treatment and for which there is no time to obtain IRB approval [21 CFR 56.102(d)]. **Life-Threatening** is defined [FDA Information Sheets] as diseases or conditions with a high likelihood of death unless the course of the disease is interrupted. **Severely Debilitating** is defined as diseases or conditions that cause major irreversible morbidity.

Emergency Use must meet **all** of the following criteria:
1. a life-threatening/severely debilitating condition in which no standard acceptable treatment is available
2. an IRB approved protocol is not available
3. an investigational agent or device that might be beneficial, in the physician's opinion in available

4. a sponsor who can provide the agent and will work with the FDA is available
5. an emergency situation exists in which there is not sufficient time to obtain FDA or IRB approval to use

Emergency use meeting the above criteria is exempt from prior IRB review and approval provided such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. Some manufacturers will agree to allow the use of the drug, biologic or device but require a letter from the IRB acknowledging the emergency circumstances but this should not be construed as IRB approval. Even for Emergency Use informed consent should be sought. Following the emergency treatment, the physician is required to provide the IRB with a report of the patient's course and final outcome.

Emergency Use IDE/IND: In some cases the emergency use of an unapproved investigational device, drug or biologic can be managed through an Emergency Use IND or IDE that is organized between the manufacturer and the FDA. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND/IDE.

The Emergency Use IND/IDE differs from Emergency Use in that it involves a mechanism already created by the FDA and manufacturer who have anticipated that these situations may arise. The manner of requesting the Emergency Use IND/IDE are the same as outlined in the Emergency Use section of this policy and the reporting requirements are also the same. With an Emergency Use IND/IDE sponsors may be allowed to collect safety data that is then shared with the FDA.

Single Patient IND/IDE or Treatment IND/IDE: The Single Patient IND/IDE, also called the Treatment IND/IDE, is a regulatory mechanism for providing eligible subjects with investigational drugs or devices for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND/IDE may be granted after sufficient data have been collected to show that the drug/device "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment IND/IDEs also serve to expand the body of knowledge about the drug or device.

Treatment IND/IDE studies require prospective IRB review and informed consent. In most cases, the Treatment IND/IDE will be established outside of a single case but will be instituted for a class of patients where the need for such a treatment can be anticipated in advance.

The IRB may choose to review each case as it occurs or may simply request a follow up report on each case either as they occur or at specified intervals under Continuing Review.

Group C Protocol: The "Group C" treatment IND was established by agreement between FDA and the National Cancer Institute (NCI). The Group C program is a means for the distribution of investigational agents to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are generally Phase 3 study drugs that have shown evidence of relative and reproducible efficacy in a specific tumor type. They can generally be administered by properly trained physicians without the need for specialized supportive care facilities. Group C drugs are distributed only by the National Institutes of Health under NCI protocols. Although treatment is the primary objective and patients treated under Group C guidelines are not part of a clinical trial, safety and effectiveness data are collected. Because administration of Group C drugs is not done with research intent, FDA has generally granted a waiver from the IRB review requirements. Even though FDA has granted a waiver for these drugs, at Legacy all Group C Protocols require prospective IRB review and approval.

13. GENETIC RESEARCH

The Legacy IRB must review all proposed genetic research. This category of research includes predisposition testing, pharmacogenetic studies and gene therapy. All three types of studies share issues of confidentiality.

Predisposition Testing: When investigators attempt to document and study the natural history of an inherited disease they do so by identifying individual members of families presenting the disease. In some instances this type of research may reveal information about an individual or family member which may not have been known. Review of these studies needs to concentrate on issues of confidentiality and the manner in which unknown information is revealed to the patient and their family. The familial nature of these studies pose challenges to minimize coercion or undue influence.

Pharmacogenetic Studies: These studies involve analysis of DNA is done in conjunction with drug studies to determine whether certain subpopulations of patients may benefit more from the drug or if a subpopulation is more likely to experience an increase in side effects. Such studies should always be optional and require a separate consent form.

Gene Therapy: As opposed to the first two categories of genetic research, these studies have a therapeutic intent. In most cases this involves the insertion of DNA into a patient using a vector, usually a virus. Gene therapy studies are reviewed like drug/device studies but with different safety factors.

Left over Blood for Unknown Research: In some clinical trials more blood is drawn than is needed and investigators or sponsors may request that they keep the serum for future use. Review issues include confidentiality and incidental findings. Ideally, the protocol should have a plan for de-identification that will not allow for linking the patient to the sample. If identifiers are maintained, there should be a justification and a plan for communicating incidental findings to the subject and/or their relatives.

14. DEFERRAL OF REVIEW TO A CENTRAL OR EXTERNAL IRB

In the conduct of cooperative research projects, each institution (or entity) is responsible for safeguarding the right and welfare of human subjects and for complying with applicable regulations. Federal regulations allow for cooperative research projects which involve more than one institution. To avoid duplication of review efforts by IRBs, the IO can choose to conduct joint reviews or rely upon the review of an External or Central IRB. The determination about whether or not to cooperate with an External or Central IRB is made initially by the Institutional Official with confirmation by the IRB Chair or Vice-Chair.

Responsibilities of the External or Central IRB:

1. Perform initial reviews and make a decision to approve or disapprove the study.
2. Maintain and make accessible to the Legacy IRB the initial protocol, protocol reviews, approvals and disapprovals and minutes of IRB meetings.
3. Carry out Continuing Reviews, reviews of Serious Adverse Events, reviews of protocol amendments, and reviews of DSMB reports. These documents will be maintained and made accessible to the Legacy IRB.
4. Maintain an IRB that satisfies the requirements of the Common Rule and provide special expertise as needed from IRB members or consultants to adequately access all aspects of each study.
5. Make available the roster of the External or Central IRB membership as well as the Standard Operating Procedures and policies.
6. Notify the Legacy IRB of any suspension or restriction of study activities.
7. Provide a final report to the Legacy IRB upon the completion of the study.

Responsibilities of the Legacy IRB

1. Ensure the safe and appropriate performance of the research at its institution. This includes, but is not limited to monitoring study compliance, major protocol violations and any serious adverse events. Provide a mechanism by which complaints about the research can be made by local study participants or others. Any actions taken as a result of problems that are identified should be promptly communicated to the External or Central IRB.
2. Require that investigators and other staff at Legacy who are conducting the research are appropriately qualified and meet Legacy's standards for eligibility to conduct research.
3. Notify the External or Central IRB if there is a suspension or restriction of the local investigator.
4. Provide the External or Central IRB with the name and address of the local contact person such as the IRB administrator.
5. Establish a procedure by which the local IRB receives and reviews the External or Central IRB's materials for studies to be performed at Legacy. This includes

reviewing the External or Central IRB's materials, determine if there are any local concerns, determine whether the review is acceptable to the Legacy IRB and decide whether to accept the External or Central IRB's review.

6. As appropriate add local language to consent forms approved by the External or Central IRB including the Legacy Liability Statement, reference to Legacy in regards to consequences of research subject's voluntary withdrawal from the study, and include contact local information concerning who to ask in regards to the rights of the research subjects.
7. If Legacy accepts the review of the External or Central IRB, the Legacy IRB will maintain records and evidence as to the approval, continuation and closure of the study.
8. Maintain a local IRB whose membership satisfies the Common Rule.
9. Maintain a human subjects protection program as required by DHHS' Office for Human Research Protection.
10. Ensure that local IRB members and local investigators receive initial and continuing education on the requirements of human subject's protection.
11. Maintain a Federal Wide Assurance and designate the External and Central IRB's authorization through an appropriately executed agreement.

15. ADVERSE EVENT REPORTING

The Common Rule specifies that investigators "promptly report…all unanticipated problems involving risk to human subjects". Such reporting can vary greatly depending on the nature of the study. For treatment studies an adverse event could be a treatment related side effect or any of a number of physical injuries related or unrelated to the drug or device. For studies that don't involve treatment, an adverse event could be a breach of confidentiality. Some studies define the range of adverse events that must be reported while others refer to FDA definitions as to what constitutes an adverse event that must be reported to the IRB.

Adverse Event - Any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product which does not necessarily have a casual relationship with this treatment. An adverse event can be therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product. Adverse events are routinely reported to sponsors but not to the IRB.

Serious Adverse Event -Any experience that suggests a significant hazard, contraindication, side effect or precaution and any experience that is fatal or life threatening, is permanently disabling, requires in-patient hospitalization or is a congenital anomaly, cancer or overdose, whether or not it is related to investigational drug or device therapy.

On-Site SAE - A Serious Adverse Event reported concerning a research subject enrolled in

a clinical trial whose Principal Investigator is conducting that study either in their clinic in Portland or at a LH facility.

Off-Site SAE - A Serious Adverse Event reported concerning a research subject who was enrolled at a site outside the LH.

IND Safety Report - An off-site SAE report generated by the sponsor and forwarded to the principal investigator.

DSMB - Data Safety and Monitoring Board is an organization that is responsible for analyzing adverse events in multi-site studies.

Investigators Brochure - A compilation of the clinical and nonclinical data on the investigational product which is relevant to the study of the investigational product in human subjects.

On-Site Reports: All on-site Serious Adverse Events must be reported to the LHS IRB within 10 working days. If a sponsor defines Serious Adverse Events in a different manner than specified below then a copy of that definition must be submitted and reporting will follow the sponsor's guidelines. In any case, all deaths of research subjects, whether on therapy or in followup will be reported to the LH IRB within 10 working days after the investigator becomes aware that the research subject has died. All on-site Serious Adverse Events will be acknowledged by the IRB chair or vice-chair.

Off-site Reports: Off-site Serious Adverse Event reports may be handled in a number of ways. They may be reported to the IRB individually, in groups of 10-20, quarterly or annually. Investigators are strongly discouraged from sending all IND safety reports to the IRB unless they provide information related to the representation of risk in the consent form. The LH IRB prefers to receive IND safety reports accompanied by analysis from the sponsor's DSMB.

16. PROTOCOL DEVIATIONS, VIOLATIONS and EXCEPTIONS

The protocol approved by the IRB must be followed or amended. Adherence to the approved protocol is not always possible and in some cases, especially those involving patient safety, such incidences must be reported to the IRB to help determine whether appropriate safeguards are in effect and whether the consent form provides adequate information for a subject to provide informed consent.

Protocol Deviation: A protocol deviation occurs when provisions of the protocol were not followed due to non-compliance by the research subject. Examples include missing study visits or mistakes in self-administration of drugs.

Protocol Violation: A protocol violation occurs when the investigator or other staff deviate from provisions of the protocol. Examples include failure to obtain informed consent, enrollment of subject who does not meet the inclusion/exclusion criteria, failure

to perform a required lab test, medication dispensing error, failure to follow safety monitoring plan, implementation of unapproved recruitment procedures, or over-enrollment, failure to submit continuing review application prior to the IRB expiration date or conducting any study procedures not approved by the IRB.

Protocol Exception: A protocol exception occurs when provisions of the protocol were not followed due to a decision made by the investigator or by the sponsor. Examples include subject visit occurring outside of visit window.

Deviations and Violations: Protocol deviations and violations are mistakes. These activities need to be reported to the sponsor but should only be reported to the IRB if they involved endangering the safety of the research subject or violating the rights of the research subject. Examples of reportable deviations and violations include misadministration of drugs that lead to hospitalization or impairment (permanent or temporary) or a breech of confidentiality where the subject's medical records are released to an unauthorized individual or company. Reportable deviations should be submitted to the IRB within five working days. That report should be in the form of a letter documenting the mistake and providing a process by which to prevent further similar mistakes. In some cases, violations and deviations may also result in a serious adverse report. The investigator will only receive a response to such a report if the action plan is not adequate. Major deviations and violations should be summarized in the narrative report requested at continuing review.

Exceptions: An exception may be granted in advance through a waiver by the sponsor or may be the result of a physician's decision that is in the best interest of the research subject. In those instances when adequate time exists, waivers must also be approved by the IRB. This should be done using the Modification Form. In those instances where there is not adequate time to consult the IRB, waiver must be reported within five working days. This report should be in the form of a letter documenting the waiver. If the investigator can anticipate that a similar situation may arise in the future, then they must submit a protocol amendment to be reviewed by the IRB. Exceptions that do not lead to protocol amendments should be summarized in the narrative report requested at continuing review.

Medical Monitor: Some treatment studies employ a medical monitor to provide safety oversight. In those cases medical monitors may authorize PIs to deviate from the protocol to ensure patient safety. These decisions may be made with and without the approval of the IRB. In those instances where there is no time to request a variance from the protocol, the PI must report the activity to the IRB within five working days. In other instances, when time allows, the medical monitor may make recommendations in regards to inclusion/exclusion criteria other protocol related details that should be submitted to the IRB for review and approval prior to instituting those changes.

17. INVESTIGATOR TRAINING

LH requires that all PI complete an educational tract every three years that is focused on protecting the rights and safety of the research subject. The Collaborative Institutional Training Initiative (CITI) from the University of Miami provides a research ethics education that is necessary to conduct clinical trials and to communicate effectively with the Legacy IRB. The training is tailored to the individual's role in the research study. Investigators may substitute similar educational tracts that are offered by the NIH, FDA or any other clinical trial sponsor or agency. Any individual who works with human research subjects may take the CITI training but it is responsibility of the PI to ensure that all such personnel are familiar with the material offered and maintain a record of their certification.

18. REGISTRIES AND BIOBANKING

Research utilizing patient clinical data and biological specimens hold enormous scientific potential. The IRB issues regarding registries focus primarily on confidentiality. Registries may serve a specific purpose or may be maintained to be queried for purposes that could not be anticipated at its initiation. Each research registry must be reviewed by the IRB Chair, and once approved, submitted to the Legacy Registry Committee for further legal and logistical processing. Such registries are required to submit a report for Continuing Review on at least an annual basis. Registries may be established for a single clinical practice focused on a specific disease entity or for broader purposes. A primary documentation for establishing a registry is the Standard Operating Procedure which must contain a statement of purpose as well as outlining methods of data collection and storage in order to maintain confidentiality and how the data may be used by those maintaining the registry and outline under what circumstances it may be shared with other. Consent should be sought from patients for inclusion of their PHI and/or biological specimen donation but in certain situations this requirement can be waived by the IRB. If PHI is maintained by the registry, the registry manager is responsible for de-identifying the data before sharing it with appropriate researchers. In some cases registries are maintained at LH for purposes of contributing to external comparative databases that may be used for benchmarking. In those instances the LH registry manager may have the ability to share such data with local investigators. If investigators are interested in obtaining data from a registry that includes PHI then that request cannot be authorized by the registry manager but must be submitted to the IRB. Data sets containing non-specific PHI may be shared utilizing a Limited Data Set agreement. If biological specimens are shared from the registry, they can only be transferred through an approval process that includes a Material Transfer Agreement.

19. VULNERABLE POPULATIONS

Certain groups of participants are considered to be particularly vulnerable to coercion or undue influence in a research setting. These groups, as outlined in the Common Rule are children, wards of the state, prisoners, pregnant women and fetuses, persons who are mentally disabled or otherwise cognitively impaired, and economically or educationally

disadvantaged persons. Vulnerable populations who must be protected from coercion may include patients facing life threatening diseases or who are recruited for research studies in emergency situations. Finally, the FDA regulations (21CFR50.24) allow for research studies involving participants in emergency settings who are unconscious or otherwise incapable or providing informed consent. In reviewing research studies involving all categories of vulnerable participants, the IRB must determine that their use is adequately justified and that additional safeguards are implemented to minimize risks unique to each group.

Pregnant Women and Fetuses: Subpart B of the Common Rule, provides additional protections for research involving pregnant women. Pregnant women should not be excluded from research as participants if the risk to the fetus is minimal. If pregnant women are included in a research protocol, the informed consent must address the possible impact of the research activity on the fetus.

Researchers who conduct studies targeting conditions specific to pregnant women must obtain informed consent from both the pregnant woman and the father of the fetus, however, consent of the father is not necessary if:
• The purpose of the study is to meet the health needs of the mother.
• The identity or whereabouts of the father cannot be reasonably ascertained.
• The father is not reasonably available.
• The pregnancy is the result of rape.

Prisoners: A "prisoner" is someone who is incarcerated or under adjudication, whether an adult or a minor. Research involving prisoners does not qualify for exemptions from IRB review. Subpart C of the Common Rule provides additional safeguards for prisoners since "Prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and un-coerced decision whether or not to participate as participants of research." In addition the general requirements for review, when reviewing research involving prisoners, the IRB reviewing the protocol must include a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. If no current member of the IRB meets the prisoner or prisoners' representative criteria, then the IRB Chair will identify and recruit a qualified individual to fulfill this requirement and advise the IRB. A PI may not enroll a prisoner in an ongoing IRB-approved study without the approval of the committee. If a participant becomes a prisoner during the course of a research study, the IRB must be notified.

Children: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." IRBs reviewing research involving children must include members who serve as advocates for that population based on their education or profession. Subpart D of the Common Rule classifies research involving children into four categories:

1. research with no greater than minimal risk

2. research involving more than minimal risk but is justified by the anticipated benefit, and the relation of the anticipated benefit to the risk is at least as favorable as that presented by alternative approaches
3. The research is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition, and the risk represents a minor increase over minimal risk, and the research presents experiences reasonably commensurate with those inherent in the participant's actual or expected medical, psychological, social or educational setting.
4. The research otherwise not approvable, but presents an opportunity to understand, alleviate or prevent a serious child health problem.

The first three categories may be approved by the IRB with special consideration to such issues minimizing risk, seeking parental permission and child assent, whether both parents' permission must be obtained, or whether the child may consent to the research without parental permission. Research described by category four must be forwarded to the HHS Secretary for review prior to IRB review.

Cognitively Impaired: Research involving participants with diminished decision-making capacity will not be considered for exemption or expedition and must be reviewed by the full board. In addition, such projects must specifically address how an individual's capacity to give informed consent will be determined. Examples of diminished decision-making capacity include: diagnosed mental retardation, some forms of mental illness, dementia, and coma, whether temporary, progressive or permanent. If an individual alternates between periods of mental competence and incompetence the PI should obtain consent from the individual as provided and ask permission from the individual to obtain consent from a relative or other person who could otherwise grant legal consent for treatment in event that the individual becomes incapable of continuing to make informed consent decisions in the future. If an individual asks to withdraw from a research study at any time: His or her participation in the research study must terminate, even if the investigator does not believe the individual to be competent to make informed decisions and even if a second opinion or third party consent has been obtained.

Economically or Educationally Disadvantaged: For research involving economically disadvantaged participants, special care must be taken to assure that any financial incentives offered do not represent the sole grounds for the individual's participation in the research protocol. Financial incentives should also not be used to encourage participants to assume risks that they would not ordinarily incur.

Employees and Students as Participants: In many research studies employees or students are recruited as participants. PIs should be aware of possible coercion when using employees or students in their research. For example, if employees or students believe their participation (or lack of participation) will be made known to someone who holds power over his or her employment or academic status, the employee or student may perceive coercion. How the PI plans to handle potential problems of coercion and undue influence must be addressed when the study is submitted to the IRB.

Exemptions from Consent in Emergency Research: In 1996, the FDA developed specific regulations (21CFR50.24) to permit research without prospective consent under carefully controlled circumstances. This is in recognition of the unique nature of emergency medical situations in which patients or family members cannot give informed consent before treatment as well as the need to allow emergency care to advance through research. According to FDA regulations, to qualify for an exception from informed consent:

- The research study must involve participants suffering from a life-threatening disease process or injury for which the current standard of care is associated with a very high failure or mortality rate.
- In addition, there must be reasonable evidence that the research has the potential to provide real and direct benefit to the patient.
- Furthermore, studies must be held to the highest ethical standards. These clinical trials undergo multiple independent rigorous reviews to ensure that they meet these standards.
- Before any patients are enrolled, communities are consulted about participation and made aware that informed consent will not be obtained for most study participants, as required by law.
- Surviving patients and/or their authorized representatives need to be informed about the trial as soon as feasible after the intervention has been given.