

STANDARD OPERATING PROCEDURE

LEGACY IRB 2015

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.

The origins of human subjects protection regulations are based on international standards such as the Nuremberg Code, the Geneva Convention and the Helsinki Accords. In the United States the regulatory framework was created with the drafting of the Belmont Report in 1978. Because of its involvement with the National Institute of Health, Good Samaritan established an IRB in 1981 while Emanuel established an IRB in the late 1980s due to its physician's use of products regulated by the Food and Drug Administration (FDA).

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. Federal regulations include 45CFR46 (HHS) and 21CFR50 (FDA). OHRP provides oversight through the assurance process and education while FDA provides oversight through audit. The Legacy IRB has been audited by the FDA in 1996, 1999, 2008 and 2014.

The objective of this SOP is to aid investigators and their staff in understanding their obligations and responsibilities in conducting human subjects research. 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. Regulatory training is available for any Legacy staff at the Collaborative Institutional Training Initiative at the University of Miami. For more information go to: <https://www.citiprogram.org/> and create an account with Legacy Health.

If you have any questions concerning the Legacy IRB SOPs you may contact Senior Research Regulatory Specialist, Paul Newton, JD, CIP at 503.413.0224 or by e-mail at PWNewton@lhs.org.

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1. IRB REVIEW PROCESS

Membership

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.

Review of studies involving children

Children are a vulnerable population who require additional protections when involved in research. Those protections must include attention to specific issues in the IRB review of research that involves children as well as the circumstances and methods of recruiting and obtaining parental permission and a child's assent to involvement in research (45CFR46 Subpart D & 21CFR50 Subpart D).

The vulnerability of children as research subjects stems from a number of factors including the fact that children commonly lack mature decision making capacity, are subject to the authority of others, may defer in ways that can mask underlying dissent and their rights and interests are socially undervalued. The enrollment of children in research must be scientifically necessary, and the research interventions or procedures must present an appropriate balance of risk and potential benefits. In addition, federal regulations defer to state law regarding the age at which minors may consent to research. In Oregon, a person under 18 is considered to be a minor and may not legally consent for medical care and certain other treatments, although there are certain exceptions for emancipated and self-sufficient minors. Oregon law is silent regarding minors consenting to their own participation in research.

- **Assent** – a child's affirmative agreement to participate in research
- **Child** – a person who has not attained the legal age for consent to treatments or procedures involved in research
- **Clinical equipoise** – genuine uncertainty on the part of the expert community about the comparative therapeutic arm of a research study
- **Component analysis** – a determination as to the overall acceptability of the research involving the weighing of risks to the subject in comparison to the anticipated direct benefit evaluated individually as well as collective benefit to the population under study
- **Emancipation** – in Oregon the juvenile court may enter judgment that a minor may be released from parental or guardian control and act as an adult at age 16 (ORS 419B.558)
- **First-in-human pediatric trial** – studies of interventions that have not be previously conducted in adult populations
- **Guardian** - a person appointed by a court of law who is responsible for the care and management of a minor or child (OAR 309-114-0005(4))
- **Minimal Risk** – the probability and magnitude of harms or discomforts in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests
- **Minor increase over minimal risk** – risks that pose no significant threat to the child's health and well-being and are commensurate with the risks of interventions or procedures having been experienced or expected to be experienced in the lives of specific children with a specific disorder or condition
- **Parent** – a child's biological or adoptive parent
- **Permission** – the agreement of parent(s) or guardian to the participation of their child or ward in research as obtained in compliance with the elements of informed consent
- **Prospect of direct benefit** – that benefit which is accrued by the enrolled child as a result of the research intervention based on the structure of the intervention

- **Scientific Necessity** – those circumstances in which children are enrolled in research to answer an important scientific or public health question that cannot be answered through enrolling other subjects (competent adults or animal models)
- **Ward** – a child who is placed in the legal custody of the State or other agency, institution or entity, consistent with applicable Federal, State or local law

The IRB must first determine whether a research proposal involving children is scientifically necessary. An important scientific question may be one that has the potential to generate information that is necessary to improve the health and well being of children as individuals and to children as a class of human beings. Children should not be enrolled in research that is duplicative or unlikely to yield important knowledge applicable to children as individuals and to children as a class of human beings.

If the IRB determines that a research proposal involving children is scientifically necessary, then a determination must be made as to whether the risks to the individual child are balanced by the potential benefit to the individual child as well as to children as a class of human beings. The risks to the child must be low if there is no prospect of direct benefit to the enrolled child. Children should not be placed at a disadvantage by being enrolled in a research study either through excessive risk or by failing to receive necessary treatment or therapy. The data necessary to initiate a pediatric study must demonstrate either an acceptably low risk or a sufficient prospect of direct benefit to justify the risk. Research studies involving children that involve more than minimal risk, or a minor increase over minimal risk, cannot be justified by the importance of the anticipated knowledge. Research studies must be categorized and assessed according to whether they do or do not offer the prospect of direct benefit through the use of component analysis.

Failure to distinguish between components of a research study may result in the lack of appreciation that an intervention may not allow for the prospect of direct benefit exceeding the allowable threshold of a minor increase over minimal risk. For research involving children, ethical principles dictate that subjects must not receive an inferior treatment; i.e.; a known effective treatment should be provided. For that reason, the choice of an appropriate control group for pediatric research must be justified when there would be no serious harm from withholding a known effective treatment such as in those cases when a placebo is used. If a placebo controlled trial cannot be ethically justified, actively controlled studies trials may be an alternative. In addition, in those pediatric studies that involve a first-in-humans pediatric trial, previous in vitro, animal or mathematic studies are required to help justify the design. In those cases, the prospect for direct benefit is unknown and so the review must concentrate on the potential risks of the experimental intervention. All research involving both adult and children that involve any risk need to contain a means and method for ongoing monitoring of risk based on the degree of risk whether by a safety board or the IRB itself.

Once the IRB reviews a research proposal and approves a study involving children it must determine the level of protection provided for pediatric subjects specifying the level of solicitation of assent from children and permission from their parents or guardians. Both HHS and the FDA address research involving children in the following categories:

1. Research involving no greater than minimal risk (45CFR46.404 & 21CFR50.51) - adequate provisions made for soliciting the assent of the children and the permission of their parents or guardians
2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects (45CFR46.405 & 21CFR20.52) - the relation of the anticipated benefits to the risk is at least as favorable 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
3. Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects but likely to yield generalizable knowledge about the subject's disorder or condition (45CFR46.406 & 21CFR20.53) – the risk represents a minor increase over minimal risk meaning that they are commensurate with those inherent in their actual or expected medical, dental, psychological, social or education situations and the knowledge to be gained by the research about the subject's disorder or condition 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

There is a fourth category of research (45CFR46.407 & 21CFR20.54) that requires a special level of governmental review beyond that provided by the IRB. If the IRB believes the research does not meet the requirements for the three categories listed above but finds that it presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children it may refer the protocol to DHHS or FDA for review.

Children who are wards of the State (agency or institution) can be included in research under the third category only if the research is related to status as wards or conducted in schools or other institutions in which the majority of the children are not wards. Special protections must be applied for wards if the research involves greater than minimal risk and has no prospect of direct benefit to the individual subjects but is likely to yield generalizable knowledge about the subject's disorder or condition under category two or three. In those instances investigators must make provisions for a child advocate for each child who is a ward. Institutionalized children must not be involved in research simply because of their availability.

Generally, children should be invited to consider assenting in research studies in which their parents and physician will honor their dissent. In those instances, two documents are used; a permission form for the parent(s) to sign, and an assent form for the child to sign. The permission form is equivalent to the long consent form with all the required elements. 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 should 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 may 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.

In some cases, based on the age of the subject and specifics of an individual study, the IRB may decide that the assent should not be sought but that the consent form be signed by the parents and the research subject.

Under Oregon law minors may consent to participation in research without parental or guardian permission if legally emancipated or married, and in certain treatment circumstances.

People 15 years of age and older may give consent to research involving general medical, dental or prenatal care if the IRB determines that reasons exist for excluding parental involvement due to the nature of the study. Subject-specific determinations should also be made by study staff at the time of consent.

People 14 years or older may consent for outpatient diagnosis or treatment of mental or emotional disorders or chemical dependency (excluding methadone maintenance) by physician, psychologist, nurse practitioner, social worker or community health worker (ORS 109.675) if the IRB determines that reasons exist for excluding parental involvement due to the nature of the study. Subject-specific determinations should also be made by study staff at the time of consent.

In the conduct of a study people of any age may consent to obtaining birth control information and services (ORS 109.610 and 109. 640) and the diagnosis or treatment of venereal disease and must be informed of public health reporting requirements (ORS 109.610).

Oregon law allows for the disclosure to the parents of non-emancipated minor's consent in cases of mental health or chemical dependency treatment as well as general medical and dental care. If parents are going to be so advised, then the plan must be in the protocol and addressed in the consent form.

Studies including children who might reach the age of majority during the course of a study (including long term follow up) should also submit an "Age of Majority Short Form" to be presented to the subject upon reaching the age of majority that includes relevant details about their ongoing participation in the trial. Consent should be sought from subjects who reach the age of majority during their ongoing treatment.

IRB Voting for Initial and Continuing Review

Federal regulations state 21CFR56.107(e) "No IRB may have a member 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." IRB members must recuse themselves from participating in voting and deliberations of studies in which they have a conflict of interest. This SOP provides guidance as how to manage and document those circumstances in which an IRB member has a conflict of interest in studies under initial review as well as continuing review. In addition, this SOP defines the quorum requirements and provides clarification of what constitutes a majority in those cases when members recuse themselves or abstain.

- **Abstention:** When a member does not vote although they are present during the vote.
- **Quorum:** The minimum number of members necessary to conduct business; one more than half including a member whose background is non-scientific.
- **Recusal:** When a member disqualifies themselves as part of the voting body.

Conflicts of interest for IRB members arise when studies are reviewed in which a member is a principal investigator, key personnel or paid consultant for a research study under review. A conflict of interest may also arise when an IRB member has financial relations with the sponsor outside of the conduct of the study under review. 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, IRB members who are administrators may review studies that affect their departments and IRB members who are physicians or nurses may be involved in reviewing studies conducted by their office partners if they are not named co-investigators or key personnel. If members feel they have a potential conflict of interest it should be stated prior to their review. Once disclosed, the IRB decides whether the potential conflict should prohibit the member from voting or participating in the review. An individual may abstain due to their inability to vote in favor of a study. They might also abstain due to the fact that they have an association with the investigator or sponsor, but that association does not constitute a conflict of interest and require their recusal. An individual who abstains from voting is still counted as part of the quorum. An individual who recuses themselves due to a conflict of interest does not count towards the quorum. Individuals who recuse themselves may attend the meeting to answer questions but must leave the room prior to deliberation and voting. The IRB must ensure that quorum is maintained when a member recuses themselves due to a conflict of interest.

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.

2. 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.

3. 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.

4. 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.

5. 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 withdraw 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.

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.

6. NON-ENGLISH SPEAKING SUBJECTS

In some cases individuals who do not speak English as their primary language and who have limited ability to read, speak, write, and understand English may directly benefit from enrollment in a clinical research study. Department of Health and Human Services (45CRF46) and U.S. Food and Drug Administration (FDA) (21CFR50) require that investigators present subjects with an informed consent document that is written in a language that they understand.

When individuals who do not understand English are to be enrolled in a clinical study, IRBs and investigators must ensure that the information given to such prospective subjects or their legally authorized representatives (LAR) is in language understandable to the subjects or their LAR. *Understandable* means the information presented in a language and at a level they can comprehend, including an explanation of scientific and medical terms.

The IRB must review and approve all English and non-English language versions of any consent documents (long form or short form) that are to be used by investigators to document the informed consent of subjects.

Individuals who do not understand English may ask or be asked to participate in a clinical trial in locations where English is the predominant language. The investigators and the IRBs that review such research should carefully consider the ethical ramifications of enrolling or excluding potential subjects when a language barrier may exist between the investigator(s) and some of the potential subjects. Consistent with the requirement that selection of subjects be equitable, individuals should not routinely be excluded from participating in research simply because they do not understand English.

Initial Application

When investigators reasonably expect that the subject population for a proposed study will include individuals who do not understand English and can anticipate the specific language(s) that they will understand, the investigator should submit to the IRB, with its initial review, appropriately translated consent documents with appropriate certification that the translation is accurate. The investigators should also provide the IRB with a description of how interpreters for oral communication will be made available to subjects during the research. For instance, an interpreter will be present throughout the consenting process including addressing questions by the patient and/or LAR. Additionally, the interpreter may also be present at study visits to address questions throughout the study and subject's participation. This is the type of detail that is required.

After initial application

If a translated consent form is not submitted with the initial application, it may also be approved as a protocol amendment in which the investigator proposes to include use of translated informed consent documents for a study already approved by the IRB. Translated consent documents may be considered no more than a minor change to the research and qualifies for an expedited review.

Use of interpreters

Informed consent is an ongoing process throughout the course of a subject's involvement in the research. It is required that whenever subjects who do not understand English are involved in research, appropriate interpreter services be made available throughout the course of the research. The use of translators in an on-going manner should be described in either the initial application or amendment that contains the translated consent form.

Circumstances when a non-English speaking participant may benefit from research but a translated consent form is not immediately available

This may occur because neither the investigator nor the IRB reasonably expected enrollment of a subject for whom a translation would be needed. For some research, the time frame for subject enrollment may provide sufficient time for the preparation and IRB review of an appropriately translated consent form. When this is the case, translated consent forms are to be reviewed and approved by the IRB prior to enrollment of the subject. In other cases the timeframe for enrollment of a subject who does not understand English may not provide sufficient time for preparation and IRB review of appropriately translated consent documents.

Generic short form

As a contingency for this situation, investigators should have prepared the translation of a generic short form in languages other than English and have prospectively approved the use of such short forms for enrollment of subjects who do not understand English, as needed for any research protocol. The generic form needs to be approved by the IRB and state that the elements of informed consent have been presented orally to the subject or the subject's LAR. Only the short form itself is to be signed by the subject or LAR while a witness or interpreter shall sign the short form and the English long form. Note, while the interpreter may serve as a witness, it is not recommended.

Obtaining informed consent prior to using a fully translated long consent form

In such circumstances, the following sequential steps must be followed as an acceptable way of obtaining and documenting the informed consent of the subject prior :

STEP ONE: The investigator, in consultation with the IRB chairperson determines that there is sufficient justification (e.g., due to a limited therapeutic window, approximately one week) for obtaining the subject's consent without waiting for a translated long form to be reviewed and approved by the IRB prior to enrollment of the subject. This consultation with the IRB chairperson should begin with a phone call but must be documented either by e-mail or written communication.

STEP TWO: Informed consent is documented using a short form that has been translated into a language understandable to the prospective subject or LAR and approved by the IRB. As a

prerequisite to using this procedure, the investigator must have available a short form written in a language understandable to the prospective subject and previously approved by the IRB. The procedure for obtaining and documenting the subject's informed consent with a translated short form and the English version of the long form, then includes the following:

- (1) The investigator obtaining informed consent, with the assistance of an interpreter, provides orally to the subject the elements of informed consent included in the IRB-approved English version of the long form. The oral presentation must be in language understandable to the subject. The investigator, with the assistance of an interpreter answers any questions from the prospective subject. There must be a witness to the oral presentation who must not be the person obtaining informed consent. Furthermore, the witness should be fluent in the language of the oral presentation.
- (2) At the time informed consent is sought, the subject is given the IRB-approved translated short form and a copy of the IRB-approved English version of the long form.
- (3) The short form is signed and dated by the subject.
- (4) The witness signs both the short form and the copy of the IRB-approved English version of the long form. (Note: the interpreter may serve as the witness, but is not required to do so.)
- (5) The person actually obtaining consent signs the copy of the IRB-approved English version of the long form.

STEP THREE: After the subject has been enrolled in the research, the investigator must promptly, within one week, obtain a translated copy of the IRB-approved English version of the long form, which served as the written summary. The investigator promptly, within one week, submits it to the IRB for review and approval. Once the translated long form/written summary is approved by the IRB, the investigator provides it to the subject. At that time, through an interpreter, the subject is asked to reaffirm their consent to continue participation in the study and sign the form along with the investigator.

In those instances where the investigator feels that it is in the non-English speaking patient's best interest to receive an experimental treatment and consultation with the IRB chairperson is not possible, or a generic short form in the subject's language is not available and there no time to create one, then they should use their clinical judgment, treat the patient and then 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.

7. 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.

8. 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

9. 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.

10. 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.

11. 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 is 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. In addition, subjects in non-treatment studies, such as behavioral studies, may experience adverse events which do not involve physical injury but result in violations of a subject's rights.

Adverse Event - Any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product which does not necessarily have a causal 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. In some cases, such as in a behavioral study, an adverse event may involve a breach of confidentiality or some other unintended violation of a subject's rights.

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 of the PI becoming aware of the event. If a sponsor defines Serious Adverse Events in a different manner than specified by the Legacy IRB then a copy of that definition must be submitted in the initial application and the IRB will determine whether reporting will follow the sponsor's guidelines. SAEs outside of the direct period of treatment may be reported on Continuing Review unless the SAE leads to a change in the protocol or consent form. Reporting procedures for SAEs in treatment trials that do not involve investigational drugs (IND) or investigational devices (IDE) should be specified in the IRB application and the IRB will determine whether reporting will follow those guidelines. In those instances where an adverse event occurs that involves a subject's rights, such as a breach of confidentiality, the PI should contact the IRB Chair to determine whether it is of a serious nature and needs to be reported immediately or is not considered serious and may simply be reported on Continuing Review. 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. If the off-site SAE does not affect the protocol or consent form, they do not have to be sent to the Legacy IRB. If the sponsor requests that they be submitted they may be reported to the IRB individually, in groups of 10-20, monthly, 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. Investigators and sponsors may negotiate with the Legacy IRB with the initial application or with an amendment in regards to submission and acknowledgement of off-site SAEs based on the nature of the study and the condition of the subjects.

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 breach 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 of 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.

LEGACY HEALTH IRB POLICY

ADMINISTRATIVE

Policy #: 100.18
Origination Date: 12/93
Last Revision Date: 1/2014

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SECTION: ADMINISTRATION/MANAGEMENT
TITLE: BIOMEDICAL AND CLINICAL RESEARCH - HUMAN SUBJECTS' PROTECTION, INSTITUTIONAL REVIEW BOARD AND USES AND DISCLOSURES OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

PURPOSE:

1. To assure the conduct of all research activities and reviews of studies involving human volunteers and patients within Legacy Health are uniform, and in compliance with all applicable policies, regardless of funding source or relationship of the research investigator to the institution.
2. To ensure protection of human subjects in biomedical and clinical research.
3. To assure that studies involving the use of human subjects are in full compliance with the policies and regulations of Legacy Health, the Department of Health and Human Services (DHHS), the Federal Food and Drug Administration (FDA), and Oregon State Law.
4. To assure that all research proposals which involve human subjects are without exception reviewed by the Legacy Institutional Review Board (IRB).
5. To establish the conditions under which protected health information ("PHI") may be used or disclosed by Legacy Health for research purposes.

DEFINITIONS:

1. **Human Subject** – A living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, or (2) individually identifiable information.
2. **Institutional Review Board (IRB)** – A board 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 and federal regulations.
3. **Interaction** – Communication or interpersonal contact between investigator and subject.
4. **Intervention** – Physical procedures by which data is gathered and manipulations of the subject or the subject's environment that are performed for research purposes.
5. **IRB Approval** – The determination of the IRB that the research has been reviewed and may be conducted at Legacy within the constraints set forth by the IRB and by other institutional and Federal requirements.

6. **Minimal Risk** – The probability and magnitude of harm or discomfort anticipated by 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.
7. **Protected Health Information** – 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.
8. **Research** – A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

POLICY:

A. Responsibilities

1. Legacy Health, as a participant in research involving human subjects shall:
 - a. Be guided by the ethical principles regarding all research involving humans as subjects as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report").
 - b. Adopt the broad tenets of the Declaration of Helsinki as institutional policy in protecting the rights and welfare of research subjects.
 - c. Encourage continuing constructive communication between the IRB and the research investigator as a means of safeguarding the rights, safety, and welfare of human subjects.
 - d. Have available the necessary resources required for human subjects who may suffer physical, psychological, or other injury as a result of participation in research activities.
 - e. Acknowledge that it will bear full responsibility for the proper performance of all work and services including the use of human subjects under federal grant or contract covered by the general assurance, including compliance with pertinent federal, state or local laws,

- particularly those concerned with informed consent and the use or disclosure of protected health information (“PHI”) for research purposes.
- f. Maintain all documentation of informed consent, authorization and waiver of authorization as it pertains to research activities conducted within Legacy Health.
 - g. Have the right to disapprove the conduct of a research study in spite of IRB approval. However, Legacy Health may not approve a research study which the IRB has not approved.
 - h. Review requests for the retrospective review of medical records applying the minimum necessary requirements as set forth in 700.15 and in accordance with 700.17, Use and Disclosure of PHI Through Internal and External Data Registries/Repositories.
 - i. Review requests for the creation or establishment of Registries/Repositories as specified in Policy 700.17.
2. Legacy Clinical Research & Technology Center (“Legacy Research”) shall implement policies, rules, regulations and procedures for the proper safeguarding of the welfare of human subjects participating in all forms of research tests and evaluation at Legacy Health.
 - a. Maintain appropriate and informative records of the IRB's review of applications, activities, of documentation of informed consent, authorization and waiver of authorization, documentation that may pertain to the selection, participation and protection of subjects, and to the review of circumstances that adversely affect the rights or welfare of individual subjects.
 - b. At least annually, reaffirm through appropriate administrative overview that its practices and procedures designed for the protection of the rights and welfare of human subjects are being effectively applied and are consistent with the regulations and assurances as accepted by federal, state and local agencies.
 3. Legacy Research, as the research arm of Legacy Health, will establish and maintain an Institutional Review Board competent to review projects and activities that involve human subjects. The responsibilities of the IRB are detailed in Attachment #1 of this policy.

B. Legal Considerations

1. Members of the IRB are responsible for familiarizing themselves with the statutes, regulations and common law precedents which may govern their duties and responsibilities hereunder through consultation with legal counsel.
2. The provisions of this policy may not be construed in any manner or sense that would abrogate, supersede or moderate more restrictive applicable law or precedential legal decision.

C. Informed Consent

No research involving human subjects may be conducted unless (1) an informed consent to participate in the research study is obtained from the research subject; or (2) a waiver of informed consent has been approved by the IRB.

D. Privacy Rule

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 Legacy Health that: (i) the use or disclosure is sought solely for such purposes, (ii) no protected health information will be removed from Legacy Health'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 Legacy Health that the use or disclosure is sought solely for research on the protected health information of decedents, (ii) provides to Legacy Health, upon request, documentation of the death of the research subject, and (iii) represents to Legacy Health that the protected health information is necessary for the research.

PROCEDURES:

1. **Informed Consent.** Informed Consent is the process by which information is presented to an individual to enable such individual to voluntarily decide whether or not to participate as a research subject. An informed consent is documented by the use of a written consent form approved by the IRB and signed by the subject. Such consent form will be provided to a subject in the following manner prior to such subject's participation unless a waiver of informed consent is approved by an IRB:
 - i. **Written.** A written consent document that embodies all of the elements set forth in Part 1.a below is signed by the subject, a copy of which is given to the subject. Informed consent presented orally to the subject or the subject's legal representative shall not be effective for medical research studies at Legacy Health.
 - a. **Informed Consent Criteria.** The informed consent shall be written in understandable language and contain the following criteria:
 - (1) a statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of experimental procedures;
 - (2) a description of reasonably foreseeable risks and discomforts to the subject;
 - (3) a description of any benefits to the subject or to others which may be reasonably expected from the research;

- (4) a disclosure of appropriate alternative treatments that might be advantageous;
 - (5) a statement describing the extent to which the confidentiality of records will be maintained;
 - (6) an explanation of whether compensation will be paid and if injury occurs, whether treatment is available and where further information may be obtained;
 - (7) an explanation of whom to contact about the research, the subject's rights and any research related injury; and
 - (8) a statement that participation in the research study is voluntary, and refusal to participate or discontinuance with the study carries no penalty or loss of benefits to which the subject is otherwise entitled.
- b. Additional Criteria. The informed consent should also provide one or more of the following provisions when applicable:
- (1) a statement that the treatment or procedure may involve currently unforeseeable risks to the subject (or to the embryo or fetus for subjects who are or may become pregnant);
 - (2) anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - (3) any additional costs to the subject that may result from participation in the study;
 - (4) the consequences of a subject's decision to withdraw from the research and procedures of how a subject may terminate his or her participation;
 - (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; and
 - (6) the approximate number of subjects involved in the study.
- c. Exculpatory Language. The informed consent shall not contain any exculpatory language or release of Legacy Health, an investigator, sponsor or other institution.
- d. Form. Legacy Health's Compound Consent and Authorization form can be found in Legacy Public Folders under System Wide – Research.
2. Authorization: In addition to informed consent under Part 1.a above, for uses and disclosures of protected health information for research purposes under the Privacy Rule, an authorization must be obtained from the research subject unless a waiver of authorization is approved by an IRB or Privacy Board, the information is de-identified, the protected health information is disclosed in a limited data set pursuant to a data use agreement, or one of the authorization exceptions set forth above applies.
- a. When requesting an authorization from a subject, Legacy Health shall use an authorization form that contains:
- (1) a description of the information to be used or disclosed;
 - (2) identification of the persons or class of persons authorized to make the use or disclosure;
 - (3) the identification of the persons or class of persons to whom the information may be disclosed;
 - (4) an expiration date or expiration event that relates to the individual or the purpose of the disclosure, which expiration date or event may be "none", "end of research study" or similar language;
 - (5) a description of each purpose of the requested use or disclosure;
 - (6) a statement of the right to revoke the authorization in writing, procedures to revoke the authorization and exceptions to the right to revoke,
 - (7) a statement that information used or disclosed pursuant to an authorization may be subject to redisclosure and may no longer be protected by the federal privacy protections;

- (8) the signature of the subject and date; or if the authorization is signed by a personal representative of the subject, a description of such representative's authority to act for the subject;
 - (9) a statement regarding the ability or inability of Legacy Health to condition treatment, payment, enrollment or eligibility for benefits on the authorization by stating either: (i) Legacy Health may not condition treatment, payment, enrollment or eligibility for benefits on whether the participant signs the authorization when such prohibition applies, or (ii) if Legacy Health is permitted to place such conditions, then an explanation of the consequences of the participant's refusal to sign the authorization.
 - b. The authorization may be in the same document as the Common Rule informed consent to participate in research, and as any optional consent to use or disclose protected health information for treatment, payment or health care operations. Legacy Health's Compound Consent and Authorization Form can be found on Legacy's Public Folders, System Wide – Research.
 - c. The authorization must be written in plain language.
 - d. Legacy Health will provide the individual with a copy of the signed authorization.
3. Waiver of informed consent and/or authorization: When relying on a waiver or alteration of the (i) informed consent to participate in a research study and/or (ii) authorization requirements to use or disclose PHI for research purposes, the IRB (or Privacy Board, as applicable) shall document the following:
 - a. Waiver of Informed Consent. An IRB can approve a waiver of informed consent if:
 - (1) The research is to be conducted by or subject to the approval of state or local government officials, and is designed to study (i) a public benefit or service program, (ii) procedures for obtaining benefits or services under those programs, (iii) changes or alternative to those programs or procedures, and (iv) changes to payment methodology; or
 - (2) For other research purposes, (i) the research involves no more than minimal risk to the subjects, (ii) the waiver or alteration does not adversely affect the rights and welfare of the subjects, and (iii) whenever appropriate, the subjects are provided with additional pertinent information after the conclusion of their participation in the study.
 - b. Waiver or Alteration of Authorization. An IRB or Privacy Board can approve a waiver or alteration of authorization if:
 - (1) Identification of the IRB (or Privacy Board) approving the waiver or alteration and the date of the approval, documentation of the waiver or alteration, and documentation of what PHI was disclosed pursuant to the waiver or alteration, to whom the disclosure was made and the date(s) of such disclosure(s).
 - c. Criteria for Waiver/Alteration of Authorization.
 - (1) The IRB or Privacy Board shall approve the waiver or alteration of the authorization requirement only if it can document that the following criteria for the waiver or alteration have been met:
 - (i) The use or disclosure of protected health information involves no more than minimal risk to the individuals or their privacy, based on (A) an adequate plan to protect identifiers from improper use and disclosure, (B) an adequate plan to destroy the identifiers at the earliest opportunity (unless there is a health or research justification for retaining identifiers or such retention is otherwise required by law), and (C) adequate assurances that the protected health information will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research permitted under this policy.

- (ii) The research could not practicably be conducted without the alteration or waiver, and
 - (iii) The research could not practicably be conducted without access to and use of the protected health information.
 - (2) The IRB or Privacy Board shall approve the waiver or authorization only if, in addition to the documentation required by Part 3.b above, the IRB or Privacy Board includes in the waiver or alteration approval document the following:
 - (i) a brief description of the protected health information to be used or disclosed;
 - (ii) a statement that the alteration or waiver of authorization has been reviewed and approved by the IRB (or Privacy Board) under normal or expedited procedures; and
 - (iii) the signature of the Chair or other member, as designated by the Chair, of the IRB (or Privacy Board).
- 4. De-identification: Legacy Health is not required to satisfy the authorization requirement if an IRB or Privacy Board determines that the health information is de-identified. Health information is de-identified only if:
 - a. a person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable 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, or
 - b. the following identifiers of the subject or relatives, employers, or household members of the subject are removed and Legacy Health does not have any actual knowledge that the information could be used alone or in combination with other information to identify the subject:
 - (1) Names,
 - (2) Geographic subdivisions smaller than a state (except the initial three digits of a zip code if the division contains more than 20,000 people),
 - (3) All elements of dates except year (and for ages greater than 89, age unless grouped together into a single category of age 90 or older),
 - (4) Telephone numbers,
 - (5) Facsimile numbers,
 - (6) Electronic mail addresses,
 - (7) Social security numbers,
 - (8) Medical record numbers,
 - (9) Health plan beneficiary numbers,
 - (10) Account numbers,
 - (11) Certificate/license numbers,
 - (12) Vehicle identification numbers,
 - (13) Device identifiers,
 - (14) Web universal resource locators,
 - (15) Internet protocol addresses,
 - (16) Biometric identifiers (e.g., finger/voice prints),
 - (17) Full face photographic and any comparable images,
 - (18) Any other unique identifying number characteristic or code, provided, however, that a code used by Legacy Health to re-identify the de-identified information is permitted so long as the code is not derived from or related to information about the subject and Legacy Health does not use or disclose the code for any other purpose and does not disclose the mechanism for re-identification.

5. Limited Data Set: Legacy Health may use protected health information to create a limited data set, or disclose protected health information to a business associate to create a limited data set, for research purposes so long as Legacy Health obtains satisfactory assurance, in the form of a data use agreement, that the limited data set recipient will only use the protected health information for limited purposes.
 - a. A limited data set is protected health information that excludes the following direct identifiers of the subject or of relatives, employers, or household members of the subject:
 - (1) Names,
 - (2) Postal address information,
 - (3) Telephone numbers,
 - (4) Fax numbers,
 - (5) Electronic mail addresses,
 - (6) Social security numbers,
 - (7) Medical record numbers,
 - (8) Health plan beneficiary numbers,
 - (9) Account numbers,
 - (10) Certificate/license numbers,
 - (11) Vehicle identification numbers and serial numbers (including license plate numbers),
 - (12) Device identifiers and serial numbers,
 - (13) Web Universal Resource Locators,
 - (14) Internet Protocol address numbers,
 - (15) Biometric identifiers (including finger and voice prints), and
 - (16) Full face photographic images and any comparable images.
 - b. A data use agreement between Legacy Health and the limited data set recipient must:
 - (1) establish that the recipient will only use and disclose the limited data set information for purposes of research, public health or health care operations,
 - (2) establish who is permitted to use or receive the limited data set,
 - (3) provide that the recipient will:
 - (i) not use or further disclose the limited data set information other than as permitted by the data use agreement or as otherwise required by law,
 - (ii) use 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 Legacy Health any use or disclosure of the limited data set information other than as 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, and
 - (v) not identify the limited data set information or contact the subjects.
 - c. Legacy Health's sample Data Use Agreement can be found on Legacy's Public Folders, System Wide – Research.

ATTACHMENT 1

THE INSTITUTIONAL REVIEW BOARD (IRB)

1. Legacy Research will establish and maintain an Institutional Review Board competent to review projects and activities that involve human subjects. The IRB Chairperson and membership will be appointed by the Clinical Vice President of Research. The term of appointment will be at least two years and may be renewed if deemed necessary or desirable. Outgoing members are encouraged to nominate their replacement. The Clinical Vice President of Research may veto any approval granted by the IRB. In turn, the Clinical VP of Research may not approve of an activity that has been disapproved by the IRB.
2. Responsibilities of the Chairperson include, but are not limited to, expedited review of protocols and informed consent and authorization forms, review of requests to use investigational drugs in emergency/life threatening situations, retrospective medical records reviews, registries/repositories and conducting the IRB meetings.
3. The members of the IRB shall be selected to allow competent assessment of applications and proposals with regard to: the safety and protection of human subjects, compliance with national, local, and institutional policies and regulations, any applicable laws, standards of professional conduct and practice, and community standards. The IRB must be sufficiently qualified through the maturity, experience, and expertise of its members. The IRB must also show sufficient diversity in its members' racial and cultural backgrounds. The IRB shall not consist entirely of members of a single professional group, nor entirely of men or of women. The IRB shall include at least one member whose primary concerns are in non-scientific areas. In addition, the IRB shall not consist entirely of persons who are officers, employees, or agents of Legacy Health but shall include at least one member who is not otherwise affiliated with Legacy Health, and who is not part of the immediate family of a person affiliated with Legacy Health. The membership shall consist of a minimum of ten members with six members constituting a quorum of which at least one must be a non-scientific member.
4. The IRB has the responsibility to review, and the authority to approve, disapprove or require changes to all research activities involving human subjects. The IRB shall have authority to suspend or terminate approval of a research activity that is not being conducted in accordance with the IRB's decisions, conditions and requirements or that has been associated with unexpected serious harm to subjects.
5. The IRB shall approve research activities involving human subjects based on the IRB's determinations that the following requirements are satisfied:
 - a. Risks to subjects are minimized:
 - 1) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
 - 2) Whenever appropriate by using procedures already being performed on the subjects for diagnostic or treatment purposes.
 - b. Risks are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB shall consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB shall not consider the

- anticipated long-range effects of applying knowledge gained in the research as among those research risks that fall within the purview of its responsibility.
- c. Selection of subjects is equitable. In making this assessment the IRB shall take into account the purposes of the research, the setting in which the research will be conducted, and the population from which subjects will be recruited.
 - d. Informed consent will be obtained from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 21 CFR 50.20.
 - e. Informed consent will be appropriately documented, in accordance with, and to the extent required by 21 CFR 50.27.
 - f. Authorization/waiver of authorization will be obtained and appropriately documented, in accordance with and to the extent required by 45 CFR 164.508, .512, .514.
 - g. Advertising used to recruit human subjects is non-coercive and reflects truth in advertising.
 - h. Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
 - i. Make adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
 - j. The circumstances set forth above under Policy, Privacy Rule, Part 2 shall be exceptions from the requirements of this policy.
6. The IRB shall require documentation of informed consent by use of a written consent form, or may waive the requirement for the research investigator to obtain a signed consent form for some or all subjects if the IRB determines that:
- a. The research is to be conducted by or subject to the approval of state or local government officials, and is designed to study (i) a public benefit or service program, (ii) procedures for obtaining benefits or services under those programs, (iii) changes or alternative to those programs or procedures, and (iv) changes to payment methodology; or
 - b. For other research purposes, (i) the research involves no more than minimal risk to the subjects, (ii) the waiver or alteration does not adversely affect the rights and welfare of the subjects, and (iii) whenever appropriate, the subjects are provided with additional pertinent information after the conclusion of their participation in the study.
- c. When the documentation requirement is waived, the IRB may require the research investigator to provide subjects with a written statement regarding the research.
7. The IRB shall have the authority to observe or have a third party observe the consent/authorization process and the research.
8. The IRB shall determine which projects need verification from sources other than the research investigators that no material changes have occurred since previous IRB review.
9. IRB reviews shall be conducted with objectivity and in a manner to ensure the exercise of independent judgment of the members. Members will be excluded from the total review process affecting projects or activities in which they have an active role or conflict of interest.
10. The review of certain studies may be eligible for an expedited review. See Attachment #2 for criteria and procedures.

11. The IRB shall utilize the following guidelines in conducting its review of studies which involve human subjects.
 - a. All studies will be reviewed to assure that the rights and welfare of human subjects will be adequately protected.
 - b. Studies will be reviewed to determine that the protocol is adequate and relevant to the established goals and objectives of the study.
 - c. Informed consent and authorization will be obtained by use of an appropriately designed and completed form, or the conditions under which this process can be altered/waived will be defined and the documentation required will be delineated.
 - d. A majority of the IRB must approve the proposal. A rejected proposal or consent/authorization form will be returned to the Principal Investigator for correction or termination.
12. The IRB will at least annually reassure itself through internal review that its practices and procedures are being effectively applied and are consistent with federal, state and local regulations.
13. In cases of collaborative activities with other institutions where Legacy Health (LH) is the grantee or prime contractor, and LH obtains access to all or some of the subjects involved through one or more collaborating institutions, LH remains responsible for safeguarding the rights and welfare of the subjects. LH is therefore responsible for initial and continuing review of these activities. In such cases the IRB of LH shall request a concurrent review by the cooperating institutions of those portions of the protocol or activity which will involve human subjects for which the other institution has responsibilities.
14. In cases of collaborative activities with other institutions where LH is not the prime contractor, the IRB shall respond to the directions of the prime contractor without sacrificing its responsibilities for safeguarding the rights and welfare of human subjects involved at LH.
15. When the IRB accepts responsibility for review of research which is conducted by any independent investigator, Legacy Research will obtain and retain a Noninstitutional Investigator Agreement (NIA) to document the investigator's commitment to abide: (1) by the same requirements for the protection of human research subjects as does LH and (2) the determinations of the IRB.
16. The IRB Questionnaire, Consent Form Template and Data Use Agreement Template are located in the Legacy Public Folders, System Wide – Research.

CRITERIA AND PROCEDURE FOR EXPEDITED REVIEW

The eligibility of some research for review through the expedited procedure is in no way intended to negate or modify the policies of Legacy Health or the other requirements of 21 CFR 56.110.

The IRB may use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized.

The only research for which the IRB may use an expedited review procedure is that which involves no more than minimal risk to the subjects and in which the only involvement of human subjects will be in one or more of the following categories:

1. Collection of: hair and nail clippings, in a non-disfiguring manner, deciduous teeth; and permanent teeth if patient care indicates a need for extraction.
2. Collection of excreta and external secretions including sweat, uncannulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.
3. Recording of data from subjects 18 years of age or older using non-invasive procedures routinely employed in clinical practice. This includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighing, testing sensory acuity, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. It does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays, microwaves).
4. Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.
5. Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
6. Voice recordings made for research purposes such as investigations of speech defects.
7. Moderate exercise by healthy volunteers.
8. The study of existing data, documents, records, pathological specimens, or diagnostic specimens.
9. Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the research investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.

10. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.
11. Any other category specifically added to this list by the Department of Health and Human Services (DHHS) and published in the Federal Register.

Surveys are "exempt" from IRB review. An institution or sponsor may choose to have a survey reviewed by the IRB but generally that will be conducted only if the survey involves very sensitive subject matter.

Expedited review shall be conducted by the IRB chairperson or by one or more of the experienced IRB members designated by the chairperson to conduct the review.

The IRB member(s) conducting the expedited review may exercise all of the authorities of the IRB except that the reviewer(s) may not disapprove the research. The reviewer(s) shall refer any protocol which the reviewer(s) recommends be disapproved to the full committee for review. The reviewer(s) may also refer other protocols to the full committee whenever the reviewer(s) believes that full committee review is warranted.

When the expedited review procedure is used to approve a new research proposal, the IRB chairperson or member(s) conducting the review shall inform IRB members of the research protocols which have been approved under the procedure.

At a convened IRB meeting, any member may request that an activity which has been approved under the expedited procedure be reviewed by the IRB in accordance with non-expedited procedures. A vote of the members shall be taken concerning the request and the majority shall decide the issue.

In cases where research activities were initially approved under expedited procedures and subsequently reviewed by non-expedited procedures, the decisions reached at the convened meeting shall supersede any decisions made through the expedited review.

EMERGENCY USE OF INVESTIGATIONAL AGENTS

BACKGROUND: The FDA regulates the development of drugs, devices and biologicals for the treatment of disease but does not regulate physician practice. The FDA allows for physicians to treat patients with investigational agents outside of a clinical trial and this policy is written to define those various circumstances which include “emergency use”, “emergency use IND”, “compassionate use”, “single patient IND”, “treatment IND”, “Group C Protocol” and “off label use of an IND”.

AUTHORITY: Although physician practice is managed by hospitals and state medical associations, the use of investigational agents, including drugs, biologicals and devices is also governed by FDA regulations. For the purposes of this policy the following federal regulations are utilized to guide this policy: 21 CFR 50.23; 21 CFR 50.24; 21 CFR 56.102(d); 21 CFR 56.104(c); 21 CFR 56.105; 21 CFR 312.34; 21 CFR 312.35; 21 CFR 312.36

PURPOSE: Due to the complexity of medical emergencies, the Legacy IRB policy provides a framework for physicians to understand their regulatory responsibilities to the institution, the manufacturer and the FDA. Specifically, this policy seeks to address the physicians’ need to seek prospective review and approval, notification, communication with the manufacturer and the FDA and follow up requirements.

The physician may not conclude that an “emergency” exists far enough in advance of the time when treatment may be needed. Institutional and FDA approval procedures may require more time than is available. 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. Examples include blindness, loss of a limb, loss of hearing, paralysis or stroke.

Emergency Use must meet **all** of the following criteria:

6. a life-threatening/severely debilitating condition in which no standard acceptable treatment is available
7. an IRB approved protocol is not available
8. an investigational agent or device that might be beneficial, in the physician’s opinion is available
9. a sponsor who can provide the agent and will work with the FDA is available
10. 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 [21CFR56.104(c)]. When emergency treatment is initiated without IRB review and approval the patient data may not be included as research data or used in a report to the FDA. The FDA regulations do not provide for expedited approval in emergency situations. Some manufacturers will agree to allow the use of the drug, biologic or device but their policy requires “an IRB approval letter” before the test item will be shipped. If it is not possible to convene a quorum within the time available, the IRB chair or vice-chair may sign a letter acknowledging the emergency circumstances but this should not be construed as IRB approval. Even for Emergency Use informed consent should be sought. If the circumstances do not provide for the opportunity to obtain informed consent, the physician is required to submit the report within five days accompanied by the determination of an independent physician that the treatment was appropriate and that informed consent was impracticable.

In either case, whether the Emergency Use is being reported to the IRB or whether the physician is seeking a letter acknowledging the request for emergency use, the letter from the physician must contain the following information:

1. the patient’s situation is life-threatening or severely debilitating
2. no standard treatment is available
3. there is no time to obtain prospective IRB approval
4. outline of the treatment plan
5. sponsor providing the investigational agent

Following the 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.

In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23]. See Emergency use section above.

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 [21 CFR 312.34 and 312.35] are mechanisms 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 "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. There are four requirements that must be met before a treatment IND/IDE can be issued:

- 1) the drug or device is intended to treat a serious or immediately life-threatening disease;
- 2) there is no satisfactory alternative treatment available;
- 3) the drug or device is already under investigation, or trials have been completed; and
- 4) the trial sponsor is actively pursuing marketing approval.

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.

For the Single Patient or Treatment IND/IDE the following documents need to be submitted to the IRB for review:

1. Protocol
2. Investigator's Brochure
3. Consent form
4. Physician's biosketch
5. Form 1572

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 [21 CFR 56.105]. Even though FDA has granted a waiver for these drugs, an IRB may still choose to conduct a review under its policies and procedures. The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no local IRB review. At Legacy all Group C Protocols require prospective IRB review and approval.

OFF LABEL and EMERGENCY USE OF AN HUMANITARIAN USE DEVICE: Humanitarian Use Devices (HUD) are intended to benefit patients in the treatment and diagnosis of disease or condition that affect or are manifested in fewer than 4,000 individual in the United States per year. The Legacy IRB is responsible for initial as well as continuing review of the HUD. For initial review of a HUD, IRBs are required to perform a full board review. For continuing review, however, IRBs may use the expedited review procedures (21 CFR 56.110) unless the IRB determines that full board review should be performed. The IRB is not required to review and approve individual uses of a HUD, although it may do so. The IRB may use its discretion to determine how to approve use of the HUD. The IRB may approve use of the HUD, for instance, without any further restrictions, under a protocol, or on a case-by-case basis. In reviewing the use of a HUD, IRBs should be cognizant that the FDA recommends that the use of the device not exceed the scope of the indication approved in the Humanitarian Device Exemption (HDE).

Emergency use of a HUD, on-label (without prior IRB approval of the 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, a HUD may be used without prior IRB approval. The physician must report the emergency use within five days; provide written notification of the use to the IRB chair, including identification of the patient involved, the date of use, and the reason of use.

Emergency use of a HUD, off-label (after prior IRB approval of the HUD)

If the Legacy IRB has reviewed and approved a HUD and HDE, a physician faced with an emergency situation (i.e., not adequate time to obtain IDE from FDA) may use a HUD outside its approved indication.

Use of a HUD after the LH IRB has approved the use of the HUD at LH facilities

If the LH IRB has reviewed and approved the use of a HUD, a physician may use the HUD for any indication (on- or off-label) without additional IRB review if s/he determines that there is no alternative device for the patient's condition. The physician should obtain informed consent from the patient and ensure that reasonable patient protection measures are followed, such as devising schedules to monitor the patient. Such off-label uses should be reported within 5 working days to the LH IRB.

RETROSPECTIVE MEDICAL RECORD REVIEWS

When retrospective medical record review audits are conducted there are several issues to consider:

1. Confidentiality as it relates to institutional practices, specific physician practices and specific patient data, must be assured by the data collector.
 - a. Retrospective medical record reviews must be approved and conducted in accordance with 700.17, Use and Disclosure of PHI Through Internal and External Data Registries/Repositories.
 - b. Data gathering procedures must be carefully designed to ensure that only the minimum necessary information relevant to the project will be obtained per Legacy Policy 700.15.
 - c. Only a code or hospital number should be used - not the patient's name. Human subjects' names should not be disclosed to non-institutional affiliated parties. Use of patient initials and study number is to be encouraged whenever possible.
 - d. Subjects' names shall be stored in locked files.
 - e. Master codes and ciphers shall be kept in secure places, distinctly separate from encoded ciphered data.
 - f. Careful controls shall be kept on the shipment, delivery and transfer of all data, computer print-outs and files between offices and institution.
 - g. If information is gathered that could identify the patient then the investigator must first provide a justification for collecting that information and submit a plan detailing how and when that information will be de-identified.

2. What is the intent of the data collection?
 - a. Physician practice quality assurance data - does not require IRB review or approval.
 - b. Government agency - disease surveillance reports - does not require IRB approval.
 - c. Comparison of treatment modalities with intent to publish results requires IRB approval via expedited review process.

The Belmont Report

Office of the Secretary

**Ethical Principles and Guidelines for the Protection of Human
Subjects of Research**

**The National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research**

AGENCY: Department of Health, Education, and Welfare.

ACTION: Notice of Report for Public Comment.

SUMMARY: On July 12, 1974, the National Research Act (Pub. L. 93-348) was signed into law, there-by creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. In carrying out the above, the Commission was directed to consider: **(i)** the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine, **(ii)** the role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects, **(iii)** appropriate guidelines for the selection of human subjects for participation in such research and **(iv)** the nature and definition of informed consent in various research settings.

The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. It is the outgrowth of an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human subjects. By publishing the Report in the Federal Register, and providing reprints upon request, the Secretary intends that it may be made readily available to scientists, members of Institutional Review Boards, and Federal employees. The two-volume Appendix, containing the lengthy reports of experts and specialists who assisted the Commission in fulfilling this part of its charge, is available as DHEW Publication No. (OS) 78-0013 and No. (OS) 78-0014, for sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

Unlike most other reports of the Commission, the Belmont Report does not make specific recommendations for administrative action by the Secretary of Health, Education, and Welfare. Rather, the Commission recommended that the Belmont Report be adopted in its entirety, as a statement of the Department's policy. The Department requests public comment on this recommendation.

**National Commission for the Protection of Human Subjects
of Biomedical and Behavioral Research**

Members of the Commission

Kenneth John Ryan, M.D., Chairman, Chief of Staff, Boston Hospital for Women.

Joseph V. Brady, Ph.D., Professor of Behavioral Biology, Johns Hopkins University.

Robert E. Cooke, M.D., President, Medical College of Pennsylvania.

Dorothy I. Height, President, National Council of Negro Women, Inc.

Albert R. Jonsen, Ph.D., Associate Professor of Bioethics, University of California at San Francisco.

Patricia King, J.D., Associate Professor of Law, Georgetown University Law Center.

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**** Deceased.*

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes (1) intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted.

Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.

This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

Part A: Boundaries Between Practice & Research

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. (2) By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project. (3)

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

Part B: Basic Ethical Principles

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. Respect for Persons. -- Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals

lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. Beneficence. -- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: **(1)** do not harm and **(2)** maximize possible benefits and minimize possible harms.

The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite

the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children -- even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. Justice. -- Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are **(1)** to each person an equal share, **(2)** to each person according to individual need, **(3)** to each person according to individual effort,

(4) to each person according to societal contribution, and (5) to each person according to merit.

Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

Part C: Applications

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. Informed Consent. -- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless,

there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that **(1)** incomplete disclosure is truly necessary to accomplish the goals of the research, **(2)** there are no undisclosed risks to subjects that are more than minimal, and **(3)** there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited -- for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence -- especially where possible sanctions are involved -- urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.

2. Assessment of Risks and Benefits. -- The assessment of risks and benefits requires a careful array of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge

to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: **(i)** Brutal or inhumane treatment of human subjects is never morally justified. **(ii)** Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. **(iii)** When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject -- or, in some rare cases, to the manifest voluntariness of the participation). **(iv)** When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. **(v)** Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. Selection of Subjects. -- Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where

research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

[\(1\)](#) Since 1945, various codes for the proper and responsible conduct of human experimentation in medical research have been adopted by different organizations. The best known of these codes are the Nuremberg Code of 1947, the Helsinki Declaration of 1964 (revised in 1975), and the 1971 Guidelines (codified into Federal Regulations in 1974) issued by the U.S. Department of Health, Education, and Welfare Codes for the conduct of social and behavioral research have also been adopted, the best known being that of the American Psychological Association, published in 1973.

[\(2\)](#) Although practice usually involves interventions designed solely to enhance the well-being of a particular individual, interventions are sometimes applied to one individual for the enhancement of the well-being of another (e.g., blood donation, skin grafts, organ transplants) or an intervention may have the dual purpose of enhancing the well-being of a particular individual, and, at the same time, providing some benefit to others (e.g., vaccination, which protects both the person who is vaccinated and society generally). The fact that some forms of practice have elements other than immediate benefit to the individual receiving an intervention, however, should not confuse the general distinction between research and practice. Even when a procedure applied in practice may benefit some other person, it remains an intervention designed to enhance the well-being of a particular individual or groups of individuals; thus, it is practice and need not be reviewed as research.

[\(3\)](#) Because the problems related to social experimentation may differ substantially from those of biomedical and behavioral research, the Commission specifically declines to make any policy determination regarding such research at this time. Rather, the Commission believes that the problem ought to be addressed by one of its successor bodies.

