INSTITUTIONAL REVIEW BOARD

STANDARD OPERATING PROCEDURES

The Pennsylvania State University

Penn State College of Medicine

Penn State Milton S. Hershey Medical Center

Version 11/18/2009

Please Note:

If this document is printed, keep in mind that updates will be made and posted to the web as needed. Users of print versions should periodically cross-reference the web version to ensure the most current policies are being followed.

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ABBREVIATIONS

AdCIRB – Adult Central Institutional Review Board
CFR – Code of Federal Regulations
CIO – Conflict of Interest Official
CIRB – NCI Central IRB
CIRC – Conflict of Interest Review Committee
CoC – Certificate of Confidentiality
COI – Conflict of Interest
COIC – Conflict of Interest Committee
COM – College of Medicine
CPR – Continuing Progress Report form
DEP – Pennsylvania Department of Environmental Protections
DHHS – Department of Health and Human Services
DNA – Deoxyribonucleic Acid
DoD – Department of Defense
DON – Department of the Navy
DSMB – Data Safety Monitoring Board
DSMP – Data Safety Monitoring Plan
DSRC – Departmental Scientific Review Committee
EHS – Environmental Health & Safety
FDA – Food and Drug Administration
FWA – Federal Wide Assurance
GAC – GCRC Advisory Committee
GCRC – General Clinical Research Center
HIPAA – Health Insurance Portability and Accountability Act
HPA – Human Protections Administrator
HSPO – Human Subjects Protection Office
HUIC – Subcommittee on Human Use of Radioisotopes
IBC – Institutional Biosafety Committee
ICIC – Institutional Conflict of Interest Committee
IDE – Investigational Device Exemption
IND – Investigational New Drug
IRB – Institutional Review Board
NCI – National Cancer Institute
NIH – National Institutes of Health
NRC – Nuclear Regulatory Commission
NSR – Non Significant Risk
OHRP – Office of Human Research Protections
ORP – Office for Research Protections
PedCIRB – Pediatric Central Institutional Review Board
PHI – Protected Health Information
PI – Principal Investigator
PRAMS – Protocol Review and Approval Management System
PSHCI – Penn State Hershey Cancer Institute
PSHMC – Penn State Milton S. Hershey Medical Center
PSU – The Pennsylvania State University
rDNA – Recombinant Deoxyribonucleic Acid
SOP – Standard Operating Procedure
SR – Significant Risk
UIC – University Isotopes Committee
UP – University Park
USDA – United States Department of Agriculture

I. INSTITUTIONAL AUTHORITY

The Pennsylvania State University (PSU) operates a program to review all human participant research to include a wide range of biomedical and social science fields. The PSU Senior Vice President for Research and the Associate Vice President for Health Sciences Research have established six Institutional Review Boards.

Throughout this document, the use of "Institutional Officials" will refer to the PSU Senior Vice President for Research and the Associate Vice President for Health Sciences Research. The use of "Senior IRB Administration" refers to one or more of the following positions: IRB Chair, IRB Vice-Chair, Office for Research Protections (ORP) Director, Human Subjects Protection Office (HSPO) Director, ORP/HSPO Associate Director and/or ORP Assistant Director – IRB Operations. The term "IRB staff" refers to any one of the following positions: Senior IRB Administration, IRB Coordinators and/or Staff Assistants. The Human Protections Administrator (HPA) refers to the individual designated with administrative responsibility for oversight of the human protection programs on the respective campus(es). At the UP campus, the HPA is the ORP Director. At the COM campus, the HPA is the HSPO Associate Director.

University Park (UP)
Two Institutional Review Boards (IRB), located on the UP campus (UP IRBs), review and provide oversight for the Social Science IRB and the Biomedical IRB. The UP IRBs review all of the research conducted by investigators from all PSU colleges and campus locations except for PSU College of Medicine. The Senior Vice President for Research serves as the institutional signatory official with the Office for Research Protections (ORP) providing administrative support.

Office for Research Protections
The 330 Building, Suite 205
University Park, PA 16802
814-865-1775
www.research.psu.edu/orp/

College of Medicine (COM)
Four IRBs (COM IRBs), located at the Penn State Milton S. Hershey Medical Center (PSHMC) campus, review and provide oversight for biomedical and social science research studies conducted at COM and PSHMC. The Associate Vice President for Health Sciences Research is the institutional signatory official for these IRBs with the Human Subjects Protection Office (HSPO) providing administrative support.

Human Subjects Protection Office
Mail Code A115
600 Centerview Drive Hershey, PA 17033
717-531-5687
www.hmc.psu.edu/irb/

II. PURPOSE

PSU IRBs are specially constituted administrative review boards established for the purpose of protecting the rights and welfare of human participants in research. Accordingly, PSU IRBs: (1) advise investigators

in designing research studies in a manner to minimize potential harm to human participants; (2) review all planned research involving human participants prior to initiation of the research; (3) approve research that meets established criteria for protection of human participants; and (4) monitor approved research to assure human participant protection remains prominent in the foundation of the research.

Additionally, the PSU IRBs inform and assist PSU and its researchers on ethical and procedural issues related to human participants in research to: (1) facilitate compliance with relevant federal and state regulations as well as PSU policies and procedures, and (2) provide a framework suitable for continued support by government agencies, private foundations, and industry for research involving human participants at PSU.

Principal investigators (PI) conducting research share the responsibility of assuring that the rights and welfare of human participants involved in research are protected. Moreover, faculty who assign or supervise research being conducted by staff or students have an obligation to consider whether these individuals are adequately qualified to carry out duties in accordance with the highest protection of human participants during research activities.

III. GUIDING PRINCIPLES

The conduct of human participant research is highly regulated and guided by ethical considerations. First and foremost, the research review unit, collaborators and sponsors must be cognizant of the fact that human participant research is a privilege, not a right stemming from academic freedom. Researchers, the research review unit, collaborators and sponsors are obligated to conduct human participant research in ways that minimize any risks or harm to participants. The IRB review and approval process is in place to ensure that all human participant research adheres to this mandate.

Guiding principles, accepted as essential requirements for the ethical conduct of human participant research, are embodied in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research (*1979) by The National Commission for the Protection of Human Participants of Biomedical and Behavioral Research (for more information, please see http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm).

Three basic principles regarding ethical research are outlined:

1. **Respect for persons** addresses the personal dignity and autonomy of individuals, and describes additional protection for special populations with less autonomy, such as children, pregnant women, fetuses, terminally ill patients, decisionally impaired individuals, medically incompetent persons, and prisoners. This principle reflects the need for proper informed consent, which must include all the essential elements and the additional elements, if applicable, as outlined in the federal regulations.

2. **Beneficence**, “do no harm”, implies an obligation to protect human participants from harm by assessing the risks and benefits of the research. Anticipated benefits must be greater than anticipated risks to comply with this principle.

3. **Justice** requires that research participants be fairly selected through a process that involves consideration of the purpose and expected outcome of the research. Selection should include

consideration of the participant as an individual and as a member of society with regard to race, sex and ethnic group. The population of research participants should be similar to the population expected to benefit from the outcome of the research.

Compliance provides protections for human participants as mandated by applicable laws, regulations and standards of local, state and federal government agencies concerning the protection of human participants.

The University's policy for the protection of human participants Policy RA14 "The Use of Human Participants in Research" and Policy AD47 "General Standards of Professional Ethics" specify that the ethical principles and institutional requirements be met for all research involving human participants.

IV. IRB AUTHORITY

A. IRB Scope

Prior to involving human participants in research, the IRB must review and approve all human participant research carried out at PSU, or under its auspices, regardless of sponsorship. No intervention or interaction with human participants in research, including advertising, recruitment, and/or screening, may begin until the IRB has reviewed and approved the research. If the proposed research involves the use of data collected for non-research purposes, IRB review and approval is required prior to accessing the data for research purposes. If an investigator begins a non-research project and later finds that the data gathered could contribute to generalizable knowledge, the investigator must submit an application to the IRB for review and approval prior to publication or presentation of the data (e.g., journal article, poster session, public speech or presentation, or project report).

Penn State Policy RA14 defines "**human research**" or "**research involving human participants**" as:

- any activity that meets the Department of Health & Human Services (DHHS) definition of "research" and involves persons who meet the DHHS definition of "human participant", OR
- any activity that meets the FDA definition of "research" and involves persons who meet the FDA definition of "human participant."

It is the responsibility of the IRB Chair, his/her designee or the convened IRB to determine what activities constitute "human participant research."

PSU IRBs review studies when one or more of the following apply to all or part of the research involving human participants:

- The research is sponsored by PSU, COM or Penn State Hershey Medical Center (PSHMC);
- The research is conducted by or under the direction of any employee, student or agent of PSU, COM or PSHMC in connection with his or her institutional responsibilities;
- The research uses any property or facility of PSU, COM or PSHMC;
- The research involves the use of PSU's, COM's or PSHMC's non-public information to conduct human participants research;
- PSU, COM or PSHMC receives a direct federal award to conduct human participant research, even where all activities involving human participants are carried out by a subcontractor or collaborator; and/or

- The research is conducted in accordance with an assurance filed with the Office of Human Research Protections (OHRP) in which a PSU IRB is designated as the IRB of record through an established IRB Authorization Agreement.

PSU IRBs shall not review studies conducted by individuals with faculty appointments at PSU who are not employed by PSU unless a PSU IRB is designated as the IRB of record through an established IRB Authorization Agreement.

Definition of Research

"**Research**" under the DHHS regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR §46.102[d]).

"**Research**" under the Food and Drug Administration (FDA) regulations means any experiment that involves a test article and one or more human participants and that either is subject to requirements for prior submission to the FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or is not subject to requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study and clinical investigation are deemed to be synonymous for purposes of the FDA regulations. In practice, all uses of drugs or medical devices constitute "research" under this definition unless the drug or device is both approved and being used in the course of medical practice. In addition, all uses of FDA-regulated test articles in which the results will be submitted to the FDA or held for inspection by the FDA constitute "research" under this definition (21 CFR §56.102[c]).

Definition of Human Participant

"**Human participant**" under the DHHS regulations means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through an intervention or interaction with the individual or (2) identifiable private information (45 CFR §46.102[f]).

- *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture or exercise regimen) and manipulations of the participant or the participant's environment that are performed for research purposes.
- *Interaction* includes communication or interpersonal contact between investigator and participant.
- *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the participant is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human participants.

"**Human participant**" under the FDA regulations means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A participant may be either a healthy human or a patient. For medical device studies in which data will be submitted to the FDA or held for inspection by the FDA, a human participant includes a human on whose specimen an investigational device is used (21 CFR §56.102[e]).

Research on Decedents
Since the definition of a human participant is a "living" individual, research involving autopsy materials or cadavers is not considered human participant research and is not regulated by the IRB. When the research involves the protected health information of decedents, the research must comply with privacy regulations and be reviewed by the institution's Privacy Board. At COM, an application would need to be submitted to the HSPO. At UP, an application would need to be submitted to the ORP.

Research Conducted at or in Cooperation with Other Sites
Research reviewed by the IRB includes studies performed by PSU employees and students at other institutions or sites, and research performed at PSU by investigators who are not affiliated with PSU. When research reviewed by the IRB is conducted at or in cooperation with another entity, all requirements of the PSU IRB review will remain in effect for that research study. See Section V.E. for additional information.

Research conducted outside the United States
The IRB must review and approve research conducted outside the United States of America by PSU employees or students, even if the foreign research receives no U.S. government funding. Such collaborative research activities must meet ethical standards similar to those required at PSU. The IRB may approve such research, provided it determines that (1) the research conforms to proper codes of ethics (*e.g.,* the Declaration of Helsinki or the Belmont Report) and (2) the research is approved by the local ethical review authority. Requirements for the informed consent process will follow the laws and customs of the country where the research is being conducted. If a U.S. department or agency funds the research, then it is probable that the foreign research site will need to file a Federal Wide Assurance (FWA) application through OHRP. For more information, see http://ohrp.cit.nih.gov/efile/. At UP, IRB Guideline II, "International Research Involving Human Participants," provides additional guidance for research conducted outside of the United States.

Failure to Submit a Project for IRB Review
The implications of engaging in research activities subject to IRB oversight without prior review and approval are significant. Results from such studies may not be published or presented unless IRB approval has been obtained prior to collecting the data. To do so is in violation of PSU policy. It is also against PSU policy to use that data to satisfy thesis or dissertation requirements. Investigators who request approval to continue human participant research that was not previously reviewed or to use data that was collected without IRB approval face the possibility that the IRB will administratively withdraw or request the investigator administratively withdraw his/her application. The IRB cannot give post-hoc approval. The IRB will not approve applications where the investigator has attempted to circumvent IRB policies and procedures regarding human participant research by collecting data as non-research and then applying to use them as existing data. It is in the investigator's best interest to consider carefully the likelihood that he or she will want to use the data for research purposes in the future, to err on the side of caution and seek IRB review and approval prior to commencing the work.

B. IRB Authority
The authority conveyed to PSU IRBs includes the following:

- Review all human participant research studies before the involvement of participants may begin;
- Require from investigators revisions in research studies and informed consent documents as a condition for initial or continuation approval;
- Approve new research studies and the continuation of previously approved studies;

- Disapprove the initiation of new research studies, if necessary;
- Monitor the activities of approved studies, including regularly scheduled continuing review at least once every 365 days and verification of compliance with approved research protocols and informed consent procedures;
- Develop mechanisms for prompt reporting to the IRB of any planned changes in approved studies prior to the implementation of those changes;
- Develop mechanisms for prompt reporting to the IRB of events that may represent unanticipated problems involving risks to participants or others occurring in approved studies, or in other studies related in context to the approved studies;
- Suspend or terminate a previously approved study, if necessary;
- Restrict aspects of a research study for the purpose of participant protections, if necessary;
- Review and monitor the use of test articles (investigational drugs, biologics and devices) for the purpose of treating serious or life-threatening illnesses; and
- Review research studies to determine compliance with the Health Insurance Portability and Accountability Act (HIPAA) governing disclosure and use of identifiable health information.

C. Authority of Institutional Officials

The Institutional Officials are responsible for the oversight of the human research protection programs. They have the authority to review decisions of the IRB. In the case of an approval decision, should the Institutional Officials conclude that a study does not fully comply with PSU policies or obligations or for other reasons; the study may be disapproved, suspended, or terminated on behalf of the institution. In the case of a decision by the IRB to disapprove, suspend, or terminate a study, the Institutional Officials or any other officer/agency of PSU, state government, or federal government have no authority to override or reverse the decision. Suspensions and terminations by someone other than the convened IRBs are reported to and reviewed by the convened IRB.

V. IRB RELATIONSHIP TO OTHERS

A. Compliance with Federal Regulations

Title 45 CFR. 46, Protection of Human Participants, U.S. Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP)

PSU has Assurances on file with the U.S. DHHS OHRP affirming that UP and COM are in compliance with 45 CFR 46. PSHMC has a separate Assurance with OHRP and has designated the COM IRBs for the review of research under this Assurance. These Assurances set forth the policies for the protection of human participants and include the duties and procedures of the IRB's.

Title 21 CFR 50, 56, 312, 600, and 812: Food and Drug Administration (FDA)

In studies involving products regulated by the Food and Drug Administration (FDA) regulations, PSU IRBs comply with the requirements set forth in 21 CFR 50, and 21 CFR 56, and where applicable research will comply with 21 CFR 312, 21 CFR 600, and 21 CFR 812 and appropriate FDA regulations.

Title 32 CFR 219, Department of Defense (DoD) Directives (DoDD 3216.2) and Department of Navy (DON) instructions (SECNAVINST 3900.39D), U.S. Department of the Navy, DON Human Research Protection Program

In studies funded by the Department of the Navy (DON), University Park IRBs comply with the requirements set forth by the Department of Defense.

Title 45 CFR. 160 and 164: Standards for Privacy of Individually Identifiable Health Information, U.S. DHHS, Office for Civil Rights
As the designated PSU Privacy Boards for research, the PSU IRBs comply with the requirements set forth in 45 CFR 160 and 164.

Other Federal Departments and Agencies
PSU also complies with other federal regulations depending on the funding source and participants to be included in the study. For example, if federal prisoners are involved, the Department of Corrections' policies and procedures for prisoners involved in research will also be implemented.

B. Top Administration of the Institution
For matters relating to the execution of its duties and responsibilities, the IRB has direct access to the authorized Institutional Officials, or their designees.

C. Department Chairs/Heads
At COM, a signature of the department chair/head is required on all human participant initial applications confirming that the investigators within the department are qualified to perform the roles proposed for them in the research study, or qualified investigators will supervise them. Additionally, department chairs/heads assist the IRB membership process by nominating faculty and staff as prospective IRB members. With the release of the IRB eApplication in late March/early April 2009, UP will no longer require signatures on new application submissions.

Department chairs/heads are encouraged to request educational programs designed for members of their departments, and/or provide the opportunity for members to attend institution-wide IRB educational programs. The IRB will keep investigators' department chairs/heads informed of cases of investigator non-compliance. At University Park, department chairs/heads and research deans are sent approval and expiration reports upon request.

D. Research Investigators
Only one principal investigator (PI) is recognized for each study and he/she assumes ultimate responsibility for his/her research study. All official IRB correspondence is addressed to the PI. Other personnel, as designated by the PI, may also receive correspondence.

Student researchers (e.g., undergraduate or graduate students, residents, fellows, post-doctoral fellows) may serve as PI's but are required to designate a faculty advisor when submitting a research study to the IRB for review.

The IRB will help to educate investigators regarding their responsibilities to conduct research in a way that minimizes any risks or harm to participants and to comply with regulatory requirements, institutional policies and procedures. IRB staff communicate directly with the PI of each study, who in turn communicates with other investigators involved in the research. However, in the conduct of its responsibilities, the IRB may query, require responses from, or otherwise communicate directly with any personnel involved with a human participants research study, whether they are listed investigators or not, or with participants themselves. For additional information, please see Section X.D.

The IRB will notify investigators of its decision to approve or disapprove research studies or of modifications required to secure IRB approval. After disapproval actions, the IRB will provide written notification of the reasons for its decision, and will give the investigator an opportunity to respond in person, in writing, or both.

E. Research Involving Performance Sites

It is the policy of the PSU IRB to assure that appropriate approvals and/or written agreements are completed when human participant research involves performance sites. A performance site is a site where research is performed

IRB of Record

The PSU IRB may serve as an IRB of record in which a PSU investigator is responsible for the conduct, administrative, or coordinating functions of the research project. The site may not have an IRB of record or due to other circumstances request the PSU IRB to serve as their IRB of record for that particular study at that particular site. For the PSU IRB to serve as the IRB of record, the research must be conducted in collaboration with PSU and the investigator must be a PSU employee, student, or agent.

When the PSU IRB serves as the IRB of record, it is accepting the responsibility of oversight of the conduct of the research for a particular site. The details of such an agreement are outlined in an IRB Authorization Agreement. An IRB Authorization Agreement or a similar formal agreement between PSU and the other institution is the only method by which the PSU IRB serves as the IRB of record for a site, which is not a legal entity of PSU. The agreement between the relevant parties outlines specific provisions and responsibilities for each party entering into the agreement. The performance site requesting PSU IRB to serve as the IRB of record must conduct the research in accordance with the terms and conditions specified in the agreement. If the research is federally funded, the performance site must have an OHRP-approved Federalwide Assurance (FWA) of compliance.

The PSU IRB may agree to permit another federally sanctioned IRB to act as the IRB of record for studies conducted by or with the assistance of PSU personnel at the facilities of a second institution or for studies where data are not collected at PSU. This agreement requires a signed IRB Authorization Agreement and a copy of this agreement is maintained at the respective administrative areas. Senior IRB Administration are responsible for negotiating and processing these IRB agreements and for revising the OHRP Assurance to include the other institution's IRB on the list of designated IRBs.

IRB staff may interact with other institutions and their IRBs to ensure that IRB policies and procedures are followed when PSU/PSHMC employees and students perform research at other institutions, or when personnel or students from other institutions perform research at PSU/ PSHMC facilities.

IRB staff verifies that the appropriate documentation has been submitted to the IRB for approval and confirms the OHRP Assurance number and IRB registration number for the other institutions, if applicable. If incorrect or incomplete documentation is submitted, the IRB staff contacts the principal investigator for the required documentation. Copies of these approvals or written agreements are included in the study file.

Performance Sites "Engaged" in Research

A performance site becomes "engaged" in human participant research when its employees or agents (1) intervene or interact with living individuals for research purposes; (2) obtain individually identifiable

private information for research purposes; and/or (3) receive a direct federal award to support the research. See OHRP "Guidance on Engagement of Institutions in Human Subjects Research".

Regardless of financial support or funding, the PSU IRB must assure that all performance sites "engaged" in research have approval from the IRB of record for the proposed research to be conducted at the site. An IRB of record is the IRB that assumes responsibility for another institution and has an approved Federalwide Assurance on file with the Office for Human Research Protections (OHRP). The performance site "engaged" in research may have the proposed research reviewed and approved by (1) an OHRP-registered IRB or (2) the PSU IRB provided an approved IRB Authorization Agreement is on file.

If the research has federal support, then the performance site "engaged" in research must have an OHRP-approved Federalwide Assurance (FWA) of compliance. Alternatively, PSU may extend its FWA to cover a collaborating individual investigator under certain conditions using an Individual Investigator Agreement.

Initiation of research conducted at a performance site "engaged" in research is contingent on the PSU IRB receipt and review of IRB approval from the "engaged" performance site. It is the responsibility of the IRB of record and the Assurance holding institution to assure that the resources and facilities are appropriate for the nature of the research under its jurisdiction.

Performance Sites "Not Engaged" in Research

When performance sites are "not engaged" in research and have an established IRB, the investigator must obtain approval to conduct the research at the "not engaged" site from the site's IRB or provide documentation that the site's IRB has determined that approval is not necessary for PSU to conduct the proposed research at the site.

When performance sites are "not engaged" in research and the "not engaged" site does not have an established IRB, a letter of cooperation must be obtained demonstrating that the appropriate institutional officials are permitting the research to be conducted at the performance site.

PSU IRB approval to conduct research at a performance site is contingent upon receiving documentation of the performance site's IRB determination or letter of cooperation, as applicable. It is the PSU principal investigator's responsibility and the performance site "not engaged" in research to (1) assure that the resources and facilities are appropriate for the nature of the research and (2) notify the PSU IRB promptly if a change in research activities alters the performance site's engagement in the research (e.g., performance site "not engaged" begins consenting research participants, etc.).

Investigators obtain IRB approval letters or letters of cooperation for each performance site and include this documentation in the initial submission to the IRB. If all of the IRB approvals and/or letters of cooperation are not available at the time of initial submission, they may be submitted to the IRB as they are received by the PI. The investigator may begin research activities at each site as it is approved by the PSU IRB. Performance sites may be added to the research study with the submission of an amendment and the appropriate documents to the IRB for review and approval prior to beginning research activities at the new performance site. The principal investigator is responsible for notifying the IRB of performance site closures, if they occur. The PI is also responsible for maintaining current IRB documentation (e.g., approvals, continuing reviews, etc) for the performance sites throughout the course of the research.

F. Other University Committees

The IRB coordinates reviews with institutional committees as described below. None of these committees is a formal part of the PSU IRB structure, but communication between the committees and the IRB regarding status of review and/or conditions of approval occurs, when applicable.

Committees for University Park (for all colleges and campus locations except the College of Medicine)

- Institutional Biosafety Committee (IBC): The primary responsibility of the IBC is to review research activities involving the use of materials (carcinogens, pathogens, rDNA) that have the potential to pose a danger to the health and safety of the researchers, the Penn State community, and/or the nearby communities. Research using rDNA must comply with the National Institutes of Health (NIH) Guidelines for Research Involving rDNA Molecules. Anyone utilizing biohazardous materials in teaching or research at PSU must submit the appropriate "Application for the Use of Biohazardous Materials in Research" to the IBC for review and approval prior to utilizing these materials. The IBC also addresses infectious-waste disposal and the handling of human blood and tissue samples. The electronic records management system (PRAMS) is used to track both IRB and IBC applications. Applications subject to review by both committees are linked in the database. Staff of both committees discuss applications as needed prior to committee approval.

- The General Clinical Research Center (GCRC): The primary mission of the GCRC is to provide research infrastructure for investigators who conduct human participant research. Investigations carried out can include studies of normal and abnormal human function, and studies of cause, prevention, progression, and cure of diseases. The UP GCRC, together with its partner at the PSHMC, are part of a national network of similar centers funded by the NIH through the National Center for Research Resources. The GCRC Advisory Committee (GAC) reviews all studies that propose to use GCRC facilities. Each study is evaluated for scientific merit, biostatistical design, utilization of GCRC resources, and data and safety information. The deliberations of this committee are not shared with the IRB unless there are specific participant protection issues raised by the GAC. Approval by the GAC, prior to final approval by the IRB, is not required. At UP, the GCRC Coordinator and IRB staff confer as needed to resolve pertinent IRB issues. At COM, the HSPO Associate Director and the GCRC Director consult each other when specific participant protection issues are raised either by the IRB or the GAC concerning a research study. The COM investigators are responsible for sharing IRB correspondence with the GCRC.

- Individual Conflict of Interest Committee (COIC): An Individual Conflict of Interest Committee (COIC) has been established to review significant financial or business interests that may compromise or have the appearance of compromising an employee's judgment in research. The ORP Director serves as the Conflict of Interest Official (CIO) and acts as the liaison to the University's Institutional Review Board(s). The CIO has delegated the responsibility of the day-to-day management of financial conflicts involving COM/PSHMC to the Vice Dean of Faculty and Administrative Affairs, with oversight provided by the Conflict of Interest Review Committee (CIRC). An IRB member, who is not a PSU faculty member, attends meetings of the CIRC as an *ex officio* member to represent the advocacy of the COM IRB for the interests of human participants.

  The COIC and CIRC review cases in which an investigator has disclosed significant financial interests that may impact research involvement. Management strategies, such as conflict disclosure, appointment of a monitor, and/or disqualification of the investigator from participating in the study, are developed and implemented to assure that the investigator may satisfy his/her research

obligations in an objective manner and to avoid and/or mitigate concerns of bias. The COIC and CIRC provides the IRB and Institutional Officials with summarized information about the nature and amount of any significant financial interest related to human participant research along with the committee's findings and recommendations. For additional information about the COIC and CIRC, see Section XVIII.

- Institutional Conflict of Interest Committee (ICIC): An Institutional Conflict of Interest Committee (ICIC), who reports to the Office of the President, has been established to review disclosures that present or appear to present an institutional conflict of interest. The ORP Director, who serves as the COI Official and ICIC administrator, will also be the liaison to PSU's IRBs when human participant research is involved. The ICIC reviews disclosures that present or appear to present an institutional conflict of interest. The ICIC provides the IRB(s) and Institutional Officials with summary information about the nature and amount of the institutional financial interest in human participant research along with the Committee's findings. For additional information about the ICIC, see Section XVIII.

- Research Misconduct Investigatory Committees: PSU Policy RA10, "Handling Inquiries/Investigations into Questions of Ethics in Research and in Other Scholarly Activities," has been developed to handle inquiries and/or investigations into questions of ethics related to research and other scholarly activities. Upon receipt of the written allegation(s) of research misconduct, the Senior Vice President for Research, the ORP Director, and the budget executive of the area in which the accused individual is primarily employed will immediately conduct an inquiry and take all necessary steps to protect government or industrial research funds and insure that the purpose of the Federal and industrial support are being carried out.

  If it is determined from the inquiry that an investigation is warranted, the Senior Vice President for Research will appoint an ad hoc Investigatory Committee consisting of at least five tenured University faculty members, each of whom will have no conflict of interest and be competent to evaluate the questions presented to the Committee. The Committee will follow the guidance provided in PSU Policy RA10 "Handling Inquiries/Investigations into Questions of Ethics in Research and in Other Scholarly Activities." External scholars or persons with relevant expertise may be consulted by the Committee where warranted by the nature of the field or by the nature of the allegation(s). The ORP Director shall provide on-going administrative support and assistance to the investigatory committee. The ORP Director does not normally provide the IRB with updates/reports on RA10 investigations. If the IRB needs to have information from an RA10 investigation to make a decision, the Director will provide this information to the appropriate IRB staff for distribution to the IRB.

Committees for Penn State College of Medicine (COM and PSHMC)

- Institutional Biosafety Committee (IBC): The IBC is responsible for ensuring that recombinant DNA (rDNA) activities comply with the NIH Guidelines for Research Involving rDNA Molecules. The Biological Safety and Recombinant DNA Committee serves as the College of Medicine IBC. The Committee shares oversight with the COM IRB for clinical studies that involve any of the following: (1) introduction of recombinant DNA from any source into a human participant (human gene transfer); (2) transplantation or implantation into a human recipient of live cells/tissue/organs from a non-human source; and/or (3) transplantation or implantation into a human recipient of human body fluids/cells/tissues or organs that have had ex vivo contact with live, non-human animal cells, tissues

or organs. IBC approval also is required for clinical studies performed at the COM that includes rDNA products, infectious agents, or biological toxins.

The PI must submit a "Biological Safety and Recombinant DNA (BSRD) Assurance Form", the research study and other supporting documents (when applicable) to the IBC. The materials must be reviewed and approved by the IBC prior to initiating the research. The IBC notifies the COM IRB in writing of its approval of studies. A human participant study will not receive final IRB approval until it receives approval from the IBC first. The IRB Coordinator and the IBC Chair discuss and work through any issues that may arise. The deliberations of the IBC are not shared with the COM IRB unless there are specific participant protection issues raised by the IBC.

- GCRC: Please see Committees for UP – The General Clinical Research Center (GCRC) above.

- The Conflict of Interest Review Committee (CIRC): Please see Committees for UP – Individual Conflict of Interest Committee (COI) above.

- Anatomical Pathology Review: Studies involving the collection of tissue or use of pathologic specimens and/or cadavers must receive approval from Anatomic Pathology. Investigators must complete a "Use of Human Tissue for Research Form" and submit it to the Department of Pathology for approval. Following review and approval of the tissue request proposal, the original signed form will be returned to the COM IRB.

- Subcommittee on Human Use of Radioisotopes (HUIC): The HUIC operates under the auspices of the Penn State Hershey Medical Center's Radiation Safety Committee. The HUIC is charged with ascertaining that all clinical and experimental or research uses of radioactive materials and/or ionizing radiation in or on human beings conform to the currently accepted radiation protection regulations and practices, and the Penn State COM Radioactive Material Licenses on file with the U.S. Nuclear Regulatory Commission (NRC) and Pennsylvania Department of Environmental Resources (Bureau of Radiation Protection). The committee reviews studies involving x-rays, radioisotopes, and non-ionizing radiation sources, such as lasers. This committee is also approved by the U.S. Food and Drug Administration to serve as the COM's Radioactive Drug Research Committee. The HUIC notifies the COM IRB in writing of its approval of studies. A human participant study will not receive final IRB approval until it receives approval from the HUIC first.

- Clinical Trials Office: The Clinical Trials Office operates to enhance, foster, and promote organized high quality industry sponsored clinical research within PSHMC and the COM. By promoting clinical research, the Clinical Trials Office will help PSHMC to meet its mission goals of excellence in patient care, education, research and community service. The staff of the Clinical Trials Office conducts initial protocol and budget feasibility analyses for industry-sponsored research studies to identify whether a clinical trial is an appropriate study to conduct at PSHMC. Other services provided by this office include regulatory processing and advertising and recruitment packages. The HSPO does not normally provide the Clinical Trials Office with updates/reports on specific investigations unless study-related regulatory documents are being processed by the Clinical Trials Office.

- Departmental Scientific Review Committees (DSRC): The Penn State Hershey Cancer Institute (PSHCI) and other COM departments have established DSRCs that review the scientific merit, feasibility and resource utilization of proposed research. Departmental policies may require that the research be approved by the DSRC before the research is submitted to the COM IRB for initial review. The PSHCI DSRC policy requires that final IRB approval may not be granted until a study receives approval from the PSHCI DSRC. The principal investigator is responsible for submitting the DSRC approval memo to the IRB.

G. Regulatory Authorities

According to University policy, the IRB will directly contact the appropriate governmental authority at OHRP and/or FDA regarding questions or to file reports of reportable events such as (1) unanticipated problems involving risks to participants or others, (2) serious or continuing non-compliance, or (3) termination or suspension of research studies.

H. Sponsors

Unless specifically required by a sponsor, federal regulations or the IRB, no written notifications of IRB deliberations shall be provided to the sponsor of a research study by the HSPO or ORP. Principal investigators, in complying with the requirements related to their research obligations, serve as the link between the IRB and sponsor. For FDA regulated devices, communication between the IRB and FDA will occur if the IRB disagrees with a sponsor's Non Significant Risk (NSR) determination. The IRB does not deviate from institutional policies and procedures at the request of a sponsor.

I. National Cancer Institute Central IRB – Pediatric and Adult Boards

Under IRB Authorization Agreements between COM and the National Cancer Institute (NCI) Central IRB (CIRB) – Pediatric and Adult IRBs (PedCIRB and AdCIRB), the PedCIRB and AdCIRB provide IRB review for NCI-approved children and adult oncology group clinical trials conducted at COM/PSHMC. The primary functions of the PedCIRB and AdCIRB are to perform initial and continuing reviews of the study. The primary function of the COM is consideration of the local context and oversight of local performance. The COM IRB decides on a study-by-study basis whether to accept the review of the PedCIRB or AdCIRB or to conduct its own review of the study. See the "IRB Standard Operating Procedure (SOP) Addendum: Facilitated Review Procedures for National Cancer Institute Central Institutional Review Boards". The relationship between the PedCIRB and the COM IRB and the AdCIRB and COM IRB are outlined in the "Division of Responsibilities between the CIRB and Participating Local Institutions".

J. Research Participants and Others

The IRB and/or the ORP/HSPO does not routinely communicate with research participants unless participants call the ORP/HSPO with questions, concerns or complaints about their research participation. These communications are handled by qualified IRB staff or referred to the principal investigator. If a concern involves a potential non-compliance issue, it is handled according to the IRB SOP entitled, "Handling Allegations of Non-compliance". Each question or concern is taken seriously and handled confidentially. Federal law prohibits the discrimination against persons that bring forth legitimate concerns for investigation. Occasionally participants are contacted directly by the ORP or HSPO if there are questions regarding the conduct of a study.

As part of the IRB post-approval review program, the IRB, ORP or HSPO may observe the consent process or other procedures involved in a research study.

VI. MEMBERSHIP OF THE IRB

A. Appointment of IRB Members

The IRBs consist of faculty, staff, and community members appointed and selected by the Institutional Officials. IRB members serve one to three-year terms and may be re-appointed at the discretion of Senior IRB Administration. IRB members who do not adequately fulfill their responsibilities, as judged by the Senior IRB Administration, may be asked to step down from IRB membership by the Institutional Official.

IRB members are appointed and selected with varying backgrounds of expertise and experience to reflect the diverse community PSU represents. Accordingly, appointments are made to avoid potential biases that would create a board that is overly represented by any one department or area of expertise, gender or ethnicity.

B. IRB Chairs

Each IRB has a Chair appointed by the Institutional Official. IRB Chairs are respected, active members of PSU or the local community who are well informed of regulations relevant to the use of human participants in research. The COM Chair must have experience in clinical research and IRB function. The term of service is at the discretion of the Institutional Official. Whenever the Chair is not available to conduct IRB business, the Chair may assign the Vice-Chair (or another designee) to assume his/her responsibilities during the period of his/her absence. In the Vice-Chair's absence, the IRB may designate a *chair pro tem* from among the members for that meeting.

Responsibilities of the IRB Chair include: overseeing the conduct of meetings, conducting or appointing designees to conduct expedited reviews, reviewing research compliance reports, reviewing problem reports, reviewing protocol exceptions, reviewing allegations of non-compliance, and assessing conflicts of interest reported by IRB members. In addition, IRB Chairs serve as a resource for investigators and IRB members regarding issues related to PSU policies, and federal and state regulations.

To assist with the responsibilities of the IRB Chairs, the responsibilities for each action below are designated to the IRB staff and Vice-Chairs who are voting members of the IRB. Other members of the IRB may be designated on an ad hoc basis.

- Determining the type of review (exempt, expedited or convened IRB) required. To carry out this action, the IRB member must be experienced;
- Assigning IRB reviewers;
- Reviewing specific revisions to assent/consent documents that are required as conditions of approval. To carry out this action, the IRB member must be experienced;
- Conducting review of expedited studies. To carry out this action, the IRB member must be experienced.

The IRB Chair or his/her experienced designee is required to review and approve research meeting expedited criteria. The Chair considers the following criteria when determining whether an IRB member is experienced: length of service on the IRB, research experience or expertise, training relative to the expedited review categories, and/or work with the participants being studied. The Chair designates a list of experienced IRB reviewers to conduct review using the expedited procedure, which is kept on file in the ORP or HSPO. The Chair updates this list by adding or removing names from the list.

C. IRB Vice-Chairs

Whenever the Chair is not available to conduct IRB business the Vice-Chair fulfills the responsibilities of the Chair for the IRBs.

Each IRB has a Vice-Chair appointed by the Institutional Official. IRB Vice-Chairs are respected, active members of PSU or the local community who are well informed of regulations relevant to the use of human participants in research. The COM Vice-Chairs must have experience in clinical research and IRB function. The term of service is at the discretion of the Institutional Official.

D. Full IRB Members

Each IRB is composed of at least five members and must include: (1) ***at least*** one member who is not employed or affiliated with PSU and does not have an immediate family member employed or affiliated with PSU; (2) ***at least*** one member whose primary concerns are in scientific areas and (3) ***at least*** one member whose primary concerns are in non-scientific areas. In addition, each IRB that reviews FDA-regulated products (drugs, biologics, and devices) includes at least one member who is a physician. Generally, each full member is assigned one or more designated alternate members. IRB members consist of faculty, staff, and community members selected and appointed by the Institutional Official. At UP, full IRB members serve three-year terms and may be re-appointed at the discretion of the Senior IRB Administration. At COM, full IRB members serve one-year terms and may be re-appointed at the discretion of the Senior IRB Administration.

At COM, if an IRB member cannot attend a meeting, he/she is responsible for contacting the designated alternate. If an alternate member cannot attend at the request of the full member, the full member is required to notify the HSPO. Full IRB members at UP are responsible for contacting the ORP if they are unable to attend a meeting. The ORP will contact the designated alternate(s) to ensure the voting position is filled.

E. Alternate IRB Members

Alternate IRB members consist of faculty, staff, and community members selected and appointed by the Institutional Official. Alternate IRB members serve three-year terms at UP and one-year terms at COM. They may be re-appointed at the discretion of the Senior IRB Administration.

When attending an IRB meeting as a substitute, alternate IRB members receive and are expected to review the same materials as the full IRB member for whom they are substituting.

Alternate members, while strongly encouraged to attend all committee meetings, are not required to attend unless they are: (1) assigned to discuss an agenda item, or (2) requested to attend in place of a full member for whom they are listed as the designated alternate. If both the alternate and the full member attend the same meeting, only one may vote. The vote defaults to the full member unless notice is given to the IRB Chair prior to the meeting. The minutes reflect who is in attendance as a voting member and the full member that an alternate is replacing.

F. Membership Composition and Diversity

The Associate Director and Assistant Director – IRB Operations in conjunction with the Director reviews and adjusts, if necessary, the IRB membership on an annual basis to ensure that it meets regulatory and organizational requirements, and that the board has members with the appropriate knowledge and

experience necessary to provide an adequate review of the research study. At UP, membership is selected by the Associate Director and Assistant Director – IRB Operations in conjunction with the ORP Director to ensure appropriate diversity, including representation by multiple professions, diverse ethnic backgrounds and both genders, and includes both scientific and non-scientific members. At COM, diversity of membership is the responsibility of the HSPO Director and Associate Director.

The IRB includes members with varying backgrounds, and sufficient experience and expertise to promote an adequate review of human participant research. The IRB will contain at least one member who can "ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law and regulations, and standards of professional conduct and practice" (45 CFR 46.107(a)). Having access to PSU legal counsel is considered a means to ascertain acceptability in terms of law and regulations.

Because the IRB regularly reviews research involving vulnerable categories of participants such as children, pregnant women, fetuses, prisoners, students as participants and individuals with decisional impairment, the IRB staff ensures that one or more members are knowledgeable about and have experience working with these participants will be involved in the review.

The ORP/HSPO Associate Directors and Assistant Director – IRB Operations, with the support of administrative staff, are responsible for ensuring that up-to-date IRB members' rosters are maintained and changes in membership are reported to the Office of Human Research Protection.

G. Responsibilities of IRB Members

For studies reviewed by the convened IRB, responsibilities of members, whether a full member or an alternate member attending as a substitute, include (1) reviewing human participant application materials in advance of meetings, (2) arriving prepared to discuss issues related to human participant protections, (3) serving as designated reviewers when requested by the Chair or the Chair's designee, and (4) having an understanding of the specific requirements of human participant regulations. When serving as a reviewer for studies, IRB members are responsible for (1) determining that review criteria and required findings are met and (2) making a decision whether the research will be approved or forwarded for convened IRB review.

At UP, Senior IRB Administration review the performance of IRB members, at least on an annual basis, to ensure they are carrying out their responsibilities. At COM, the HSPO Director and Associate Director review the performance of IRB members before the selection of IRB membership for a new academic year, or more often if needed, to ensure members are carrying out their responsibilities.

H. Compensation of IRB Members

IRB members do not receive direct monetary compensation for participation on the board. Community members are provided parking vouchers, if applicable, to cover the cost of parking during scheduled meetings. Computer equipment may be available to members for use in reviewing studies, sending and receiving correspondence to or from the ORP/HSPO, and any matters relating to his/her appointment to the IRB. Equipment is returned upon the termination of IRB appointment. The user receives a license for the software that is currently installed on the computer. Ink and paper supplies are the responsibility of the member.

UP IRB Chairs receive an annual stipend to be used at their discretion. COM IRB Chairs do not receive direct monetary compensation above their base salary for their participation on the IRB. Rather, the departments of the IRB Chairs are reimbursed for the percentage of their effort designated to IRB responsibilities. Vice-Chairs are not reimbursed at either location.

I. IRB Member Liability

IRB members function as agents of PSU while performing duties and activities required by their appointment to the IRB. When acting in accordance with PSU IRB's policies, they are afforded coverage under applicable PSU liability insurance policies.

J. Ex-Officio Members

The IRB staff may, at his/her discretion, recruit ex-officio members from among the academic or administrative staff of PSU whose presence at an IRB meeting would aid the IRB in conducting its duties. These members may take part in IRB meetings, participate in the discussions, and make recommendations, but they may not vote on the decisions. Ex-officio members are not included in determining or establishing a quorum at the meetings. IRB meeting minutes reflect the presence of ex-officio members.

K. Consultants

At the time of review, the IRB may invite scientists or non-scientists from within or outside PSU, who have special expertise, to function as a consultant reviewer of an IRB application. This determination may be made based on the scientific design of the study, the ethical issues of the study, the potential risks or benefits of the study, specific privacy and confidentiality concerns, or considerations relative to a particular study population.

The IRB staff in conjunction with the IRB Chair are responsible for reviewing each project to determine if there is a need for a consultant review. Upon identifying the need for such a review, the IRB staff, and/or designated reviewers, in consultation with the Chair, will identify a consultant based on the particular issues to be addressed. For issues requiring only simple clarification, a written set of questions may be developed for submission to the consultant. The consultant's written response to these questions will be provided to the IRB for review at the time of the convened meeting. For issues requiring more than simple clarification, the consultant may also be invited to attend the board meeting during the review of that particular study. The consultant is not included in determining or establishing a quorum at the meetings. Consultants have access to all documents submitted to the IRB relevant to the specific study under review, and may participate in the deliberations and make recommendations on the study, but may not vote. Documentation including the attendance of and discussion with the consultant will be included in the meeting minutes as outlined above.

No person with a conflict of interest will serve as a consultant for the purposes described in this section. For more information, see Section XVIII. The IRB staff is responsible for reviewing the policy with the consultant to determine that no conflicting interest exists.

L. Guests Attending Meetings

At their discretion, the IRB staff may invite:

- Investigators, research personnel and/or advisors for the purpose of additional clarification or discussion regarding their study.

- Guests, including members of the academic or administrative staff of the PSU or COM/PSHMC, regulatory or other agencies or the community. Guests and the reason(s) for attendance are stated at the beginning of the meeting and in the minutes.

When investigators, research personnel, and/or advisors attend the meeting as guests they may participate in the discussion to provide information requested by the board. These individuals are required to leave the meeting before the final deliberation and vote on the study.

When other guests are invited to the meeting, they may observe only and may not participate in the meeting except to provide information requested by the board. Guests are not included in determining or establishing a quorum at the meetings. Guests may remain present to observe during the discussion, the final deliberation and vote for research under review, but may not make recommendations to the board or participate in the vote.

The IRB meeting minutes reflect the presence of all guests. At COM, guests sign a statement on the attendance sheet agreeing to keep confidential all information disclosed through the discussion and/or the materials for the IRB meeting. At UP, guests sign an individual guest statement.

M. Conflict of Interest

Given the central role of IRBs in overseeing the ethical conduct of research involving human participants, it is critical that IRBs operate free from inappropriate influence and bias.

IRB members, including chairs and vice-chairs, regular, alternate and ex-officio members of the board, and IRB staff must follow the conflict of interest policies outlined in Section XVIII.

Guests at IRB meetings must follow the same conflict of interest definitions that apply to IRB members as well as the IRB policy for exclusion before the deliberation and vote. See Section XVIII.

Consultants to the IRB must also follow the same conflict of interest definition that applies to IRB members, outlined in Section XVIII. However, no person with a conflict of interest may serve as a consultant.

For specific Penn State policies and guidelines, see the following:

- PSU Policy RA20 – "Individual Conflict of Interest"
- PSU Policy RA21 – "Institutional Financial Conflict of Interest Involving Sponsored Projects, Dedicated Gifts, Research, Scholarship and Technology Transfer"
- PSU Policy HR91 – "Conflict of Interest"
- Guideline RAG16 – "The Responsible Conduct of Research"
- Guideline RAG20 – "Guidance on the Disclosure of Significant Financial or Business Interest(s)"

N. Initial Training, Continuing Education and Professional Development

For the specific requirements see Section XIX.B.

O. IRB Executive Committee

At COM, a committee composed of the IRB Chairs, Vice-Chairs, experienced IRB members and designated HSPO staff members meet on a monthly basis to make policy and procedure decisions that

affect all COM IRBs. Minutes of these meetings are provided to all IRB members as part of the regular IRB meeting materials.

P. Evaluation of IRB Members and Chairs

IRB members are evaluated on an ongoing basis by the Senior IRB Administration and Chairs of the IRB. Such evaluation will occur no less than annually. IRB members complete a self-evaluation form, which is reviewed by the IRB Chair and members of the Senior IRB Administration. Performance is assessed according to the IRB member's meeting attendance records, numbers of studies reviewed, level of participation during and outside of meetings, and understanding of the regulations, ethical principles and IRB policies and procedures. When necessary, the IRB Chair or member of the Senior IRB Administration will meet privately with a member to discuss concerns about their performance. Full or alternate IRB members who do not adequately fulfill their responsibilities, as determined by the Senior IRB Administration, may be asked to resign or their membership may not be renewed by the Institutional Official.

IRB Chairs and Vice Chairs will also be evaluated on an ongoing basis by the Senior IRB Administration. Such evaluation will occur no less than annually. Chairs and Vice Chairs complete a self-evaluation form, which is reviewed by members of the Senior IRB Administration. Performance is assessed according to the same standards as members. In addition, Chairs and Vice Chairs are also assessed according to leadership ability, meeting management, engagement in the expedited review process, and effectiveness as representatives of the IRBs. The Director of ORP or the HSPO or the Institutional Official meets annually with each of the IRB Chairs for an evaluation of their performance and level of interest in continuing to serve in this capacity. A written evaluation is provided only if the Chair request it.

VII. IRB ORGANIZATION

A. University Park

Research conducted by investigators from all PSU colleges and campus locations with the exception of the COM, or using resources from these locations, must be reviewed by one of the two IRBs. Meetings are held on regular basis to review all initial research applications, modifications to ongoing research studies, continuing review reports, and events that may represent unanticipated problems involving risks to participants or others.

B. College of Medicine

All research conducted by investigators from COM and PSHMC, or using resources from the COM or PSHMC, must be reviewed and approved by one of the COM IRBs. The PSHMC has a written agreement with the COM documenting this reliance on the COM IRBs. Three of the COM IRBs meet on a regular basis to review all initial research applications, modifications to ongoing research studies, continuing review reports, and events that may represent unanticipated problems involving risks to participants or others.

The Urgent Issue IRB (Board D) is convened on an ad hoc basis, at the discretion of the HSPO Director, to respond to urgent issues. To ensure continuity and uniformity of deliberations, the Urgent Issue IRB is composed of members from the other COM IRBs. Existing studies that receive urgent action by the Urgent Issue IRB (Board D) are followed (e.g., for continuing review) by one of the IRBs that routinely

reviews issues for ongoing research. The IRBs meeting on a regular basis are notified in writing of any actions taken by the Urgent Issue IRB when relevant.

C. Referral to another PSU IRB

There is a comprehensive IRB Authorization Agreement between the COM and UP for the review of collaborative studies that include investigators or resources from the COM and other PSU locations. When a collaborative research study is submitted to either one of the IRBs, a discussion occurs between the ORP/HSPO IRB staff to determine which IRB will conduct the review. The investigator(s) cannot choose which IRB should review the protocol.

D. Administrative Support

The ORP and the HSPO have been established to facilitate and enhance the IRB process including:

- Prepare for and administratively support IRB meetings;
- Maintain files on all human participant research (including copies of all correspondence between the IRB and investigators) that take place at PSU and/or PSHMC;
- Maintain an electronic data management system (PRAMS) for tracking studies;
- Prepare meeting minutes;
- Maintain files for convened IRB meeting minutes;
- Screen research studies for completeness prior to initiating the IRB review process;
- Act as a resource for investigators on regulatory information, guidance with forms, and assistance in preparing an application;
- Maintain the institution's FWA and IRB membership records;
- Provide staff support to the IRBs for all written correspondence;
- Initiate notices of approval, study closure, continuing reviews, study suspension and termination;
- Maintain information on federal regulations relating to human participant research; and
- Provide education regarding the IRB process and regulations to the PSU community and the community at large.

E. Resources

PSU is committed to providing adequate resources (financial and personnel), facilities, and equipment to support the operation of the IRBs and performance of the functions described in this document. The Institutional Officials continue to assess the resources needed to provide a quality human participant research program to protect the rights and welfare of research participants.

PSU has an annual budget evaluation process to review and allocate resources within the institution. The Senior IRB Administration for UP and COM review and evaluate the budgetary needs for the human protection programs and prepare an annual budget for the allocation review process.

Annually, or more frequently if needed, the Senior IRB Administration for UP and COM review and evaluate whether the human participant protection offices are staffed adequately to provide oversight in a timely and professional manner. An annual assessment is also made to determine if the number of IRBs is appropriate to the volume and types of human research being reviewed, so that reviews may be accomplished in a thorough and timely manner.

VIII. IRB RECORD KEEPING AND REQUIRED DOCUMENTATION

A. Access to IRB Records

All IRB records are stored in locked offices and secure computer systems in the HSPO or ORP. Record access is limited to:

- Institutional Officials
- IRB members
- ORP and HSPO staff
- Officials of federal regulatory agencies conducting reviews such as the OHRP and FDA
- Research investigators and research personnel (reasonable access to files related to their research)
- Appropriate accreditations bodies

All other access to IRB records is limited to those who have legitimate need for them, as determined by the ORP and HSPO.

B. List of IRB Members and Qualifications

The ORP and HSPO maintain the IRB membership rosters. A list outlining IRB members for each IRB is filed with the Office for Human Research Protections (OHRP) in the Department of Health & Human Services (DHHS). OHRP is promptly notified of any changes in IRB membership. All IRB membership rosters include the following information, as required by the OHRP:

- Names of IRB members
- Names of alternate members and the corresponding regular member(s) for whom each alternate may serve
- Earned degree of each member and alternate, where applicable
- Department and area of expertise, where applicable
- Indications of experience such as board certifications or licenses that are sufficient to describe each member's chief anticipated contribution to IRB deliberations
- Representative capacity of each member or alternate, e.g., scientist or non-scientist, affiliated or non-affiliated**,** vulnerable populations
- Any employment or other relationship between each member and the institution
- Affiliation with PSU or PSHMC – an IRB member is affiliated if they or their immediate family have any affiliation with PSU or PSHMC

Up-to-date resumes or curriculum vitae of all IRB members and alternate members are kept on file in the HSPO/ORP. This information includes earned degree(s); indication of experience, such as board certification, licensures, or other relevant experience sufficient to describe each member's chief anticipated contribution to IRB deliberations; and employment or other relationship between each member and PSU or COM/PSHMC. Annual records are maintained of IRB member conflict of interest disclosure agreements and member disclosure of their affiliation and the affiliation of their immediate family with PSU or PSHMC.

At the COM, a membership list, with the specific meeting date and individual signatures indicating those members present at the meeting, is filed with each new study approved, any convened board decision or action, and with the meeting minutes.

C. Education and Training Records

Records regarding the completion of required human protection tutorials and the date are maintained for investigators and key personnel, IRB members and ORP/HSPO staff in the electronic data management system, PRAMS (Protocol Review and Approval Management System). In addition, the records and certifications for the on-line education, CITI Course: Protection of Human Research Subjects, are also archived within the CITI database.

D. Documentation of Convened IRB Meetings

Detailed minutes of each IRB meeting are kept by the IRB staff assigned to that committee. The format and subject matter comply with the federal regulations and include the following:

- Attendance at IRB meetings, including a list of members (i.e., regular and alternate) and guests, the name of alternate members replacing a regular member for the meeting and the name of the regular member replaced, and documentation of when individuals join and leave the meeting in sufficient detail to indicate the IRB members present for each vote
- Educational session topics for IRB member education or discussion
- Review of the minutes from the previous meeting
- A list of research approved since the last meeting via expedited review procedures
- Actions taken by the IRB, including the proposals and motions, deliberations and the results of each vote
- Documentation of the quorum and votes for each IRB action and determination by recording votes to denote the total number voting, number voting for, number voting against, number abstaining, and the names of any members leaving the room because of a conflict of interest along with the fact that a conflicting interest was the reason for the exclusion. The vote documentation will also reflect if an alternate member replaces a regular member for the review, deliberation and vote on a particular study only (as opposed to alternating for the regular member for the entire meeting as listed in attendance).
- Any modifications required to secure approval and the basis for requiring changes
- The basis for disapproving research
- Documentation of determinations along with study-specific findings that justify the determinations where required by federal regulations including:
    - Waiver or alteration of the consent process
    - Research involving pregnant women, fetuses and neonates
    - Research involving prisoners
    - Research involving children
    - Rationale for significant risk/non-significant risk device determinations related to Investigational Device Exemption (IDE) criteria
- A written summary of the discussion of controverted issues and their resolution, including controverted issues where the resolution is to accept the study as submitted
- Actions taken by the IRB regarding complaints, events that are determined to be unanticipated problems involving risks to participants or others, or non-compliance
- Justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in an OHRP-approved sample informed consent document that was approved by the IRB
- For initial and continuing reviews, the approval period (review interval) will be documented to reflect the determination of which studies require continuing review more often than annually, as appropriate to the degree of risk

- Membership list with member's signature indicating presence at meeting (COM only)
- Memos to investigators indicating the actions and decisions of the IRB, if applicable

Detailed minutes of each IRB meeting are kept on file. Minutes are distributed in advance and brought before the board members for approval at the next scheduled meeting.

The minutes of the COM Urgent Issue Board are distributed to its members for approval via mail or email. A written record of each member's approval or disapproval of the minutes is then filed with the minutes.

E. Documentation of Exemptions

Documentation of verified exemptions is included in the study file. The investigator's application and/or protocol summary abstract provide justification that the study meets the conditions of the cited exempt category(ies). The reviewer completes an exemption reviewer checklist and indicates the category that justifies the exempt determination. The ORP or HSPO communicates the exempt status in writing to the investigator. At COM, studies that are determined to be human participant research that are exempt from IRB oversight are reported to the IRB members at the next IRB meeting. At UP, exempt studies are available to IRB members upon request.

F. Documentation of Expedited Reviews

Documentation of expedited review is included in the study file. The investigator's application and/or protocol summary abstract provide justification that the study meets the conditions of the cited expedited review category. The reviewer completes an expedited review checklist, indicates his/her decisions and the category that justifies the expedited determination, and study-specific findings, if applicable. The IRB Chair or his/her designee may approve studies as submitted or require modifications necessary to secure approval. Disapprovals may not be rendered for studies reviewed through the expedited process. In such cases, if a reviewer does not find the study eligible for expedited approval the study must be submitted for review by the convened IRB along with the comments and recommendations of the IRB Chair or his/her designee. Approved expedited studies are subject to at least an annual review. This information is communicated to the principal investigator in the approval letter. Studies reviewed and approved through the expedited process are reported to the IRB members at the next meeting in the IRB meeting packet. In addition, at COM a copy of the protocol summary abstract with the specific citation for the categories of expedited review are provided to the board members.

G. Documentation of Emergency Use of a Test Article

Emergency use reports, which include written certifications of exceptions from informed consent for emergency use and/or exemptions from a PSU IRB review for emergency use of a test article, are kept on file in the HSPO/ORP with the investigator's request, patient information, justification of the need for the research treatment, and the IRB Chair's assessment of compliance with the regulatory requirements for the emergency use.

H. IRB Study Files

The IRB maintains a separate file for each research application (study) it receives for review. Studies are assigned a tracking number at the time of submission by PRAMS. Each file will contain documentation of the following, when and where applicable:

- Approval letter(s)
- Continuing review frequency, as noted in minutes or otherwise indicated in the file

- Correspondence
  - Copies of the minutes, if applicable, related to the issue under review
  - Correspondence to and from the IRB
  - Letters of agreement
  - Certificate of Confidentiality
  - IRB Authorization Agreement
  - Sponsor, OHRP & FDA
- Extraordinary Events
  - Unanticipated Problems
  - Other Problems
  - Conflict of Interest*
  - Non-compliance
  - Protocol Deviation
  - Safety Reports

*The IRB maintains the COI disclosures and a copy of the memo from the conflict of interest committee within the IRB submission. The conflict of interest review committee maintains the documentation for financial disclosure and activities related to the evaluation and management of disclosed financial interests.

- HIPAA Documentation
  - Authorization
  - Waiver of Authorization
  - Review Preparatory to Research
  - Decedent Research
  - Data Use Agreement
  - Business Associate Agreement
  - De-identified Data (UP only)
  - Limited Data Set (UP only)
- Informed Consent Forms
  - Adult Form
  - Parental Permission Form
  - Assent Form
  - Addendum
  - Approved DHHS or sponsor-provided sample consent documents, if any
  - Statements of significant new findings provided to participants
- Instruments
  - Surveys/Questionnaires
  - Interview/Focus group scripts
  - Data Collection forms
- Monitoring
  - Auditing Reports – internal and external
  - Data Safety & Monitoring Board (DSMB) reports
- Protocol Documents
  - Investigator-written, approved DHHS, or sponsor-provided protocol
  - Amendment
  - Investigator Brochure

  - Drug Package Insert
  - Copies of all scientific evaluations available
- Recruitment
  - Recruitment materials
  - Eligibility screening
  - Debriefing statement
- Review Documents
  - Reviewer sheet
  - Additional information request
  - PI response
- Submission Forms
  - Initial application
  - Modification requests
  - Continuing Progress Report (CPR) forms
  - Protocol Summary
  - Project Closeout form
  - Grant application

I. Protocol Review and Approval Management System (PRAMS)

The IRB maintains an electronic data management system, PRAMS (Protocol Review and Approval Management System), to assist in the administration of the review and approval process. Each research study includes at a minimum:

- Title of the research study
- Names of principal investigator and co-investigators including completed training
- Personnel associated with each study/submission including completed training
- Funding source
- Date of initial approval
- Date of most recent continuing approval
- End of current approval period
- Level of review (expedited, convened board review or exempt)
- Number of participants (# approved and # enrolled)
- Names of IRB members who completed the review of the study
- College and department responsible for the study
- Indication if review and approval of the biosafety committee is warranted (UP only)

Additionally, PRAMS automatically generates and sends continuing review notices as well as approval expiration notices to investigators. Reports can also be generated for tracking and review purposes.

J. Retention of Records

All IRB records related to research are maintained intact for at least three years following the study's completion date in accord with federal regulations and are maintained in a designated storage area or on the electronic database. Investigators are required to maintain their research records and the original signed informed consent forms for at least three years after the research terminates or two years after the information is no longer needed for drug or device approval, whichever comes last. Signed authorization forms and consent forms that incorporate authorization for the use of protected health information for research, and the tracking of disclosures of protected health information for research, must be maintained

by the principal investigator for at least six years to comply with privacy regulatory requirements. Records are accessible for inspection by authorized representatives of federal or accreditation agencies or departments.

The IRB maintains records for applications that are withdrawn and records for studies cancelled without participant enrollment for three years after cancellation or withdrawal.

IRB records not related to research but to the regulatory operations of the IRBs will be retained for at least three years. Other records not related to research or the regulatory operation of the IRBs will be retained in compliance with the Penn State policies for document retention included in the following documents: General Retention Schedule (Formerly Appendix 18); Financial Document Retention Schedule University Auditing Department Requirements (Formerly Appendix 21) and PSU Policy AD35, "University Archives and Records Management".

K. Budget and Accounting Records

Operating budget and accounting records for the ORP and HSPO will be kept by the respective offices in accordance with PSU requirements for retention of financial documents. For additional information, see PSU Policy AD35 "University Archives and Records Management".

IX. FUNCTIONS OF THE IRB

A. Determining Whether an Activity is Human Participant Research

The IRB has sole authority to determine whether an activity represents human participant research. Investigators do not have the authority to make an independent determination and must submit a request form for an IRB determination to the IRB. It is the responsibility of the IRB Chair, his/her designee or the convened IRB to determine what activities constitute "human participant research" by considering whether the activity either:

- Meets the regulatory definitions of "research" that involves "human participants, " or
- Meets the regulatory definition of "clinical investigation."

<u>Non-Research Activities</u>

- Activities are not research if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis or developing a theory.
- Activities are not research if they do not contribute to generalizable knowledge or if the results (or conclusions) of an activity are not intended beyond an internal program or individuals associated with the activity.
- Thesis or dissertation projects conducted to meet the requirements of a graduate degree are usually considered generalizable and therefore, require IRB review and approval.

<u>Non-Human Participant</u>

- Activities do not involve humans as participants if they do not involve the process of obtaining specimens or data through intervention or interaction with individual participants or identifiable private information.
- Information is considered "not identifiable" if it includes none of the identifiers enumerated in the Health Insurance Portability and Accountability Act (HIPAA; Privacy Rule).

- Activities that involve specimens/data that are received by the investigator de-identified (stripped of all HIPAA identifiers) with no code or link that would allow an investigator to establish identity are non-human participant activities.
- The investigator may receive coded private information or specimens and qualify as non-human participant if the following conditions are met:
    - The code is not derived or related to the HIPAA identifiers;
    - The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
    - The investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain, because:
        - The key to decipher the code is destroyed before the research begins;
        - The investigator and the holder of the key enter into an agreement prohibiting the release of the key to the investigator under any circumstances, until the individuals are deceased;
        - The private information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the investigator under any circumstances, until the individuals are deceased; or
        - There are other legal requirements prohibiting the release of the key to the investigator until the individuals are deceased.

The IRB chair, his/her designee, or convened IRB reviews the proposed activity to determine if the research qualifies as non-human participant research as defined in this section. The reviewer documents the determination and justification on a reviewer form. If the activity is determined to be non-human participant research, the IRB notifies the investigator in writing of its decision. If the activity is determined to be human participant research, the reviewer determines the appropriate level of review, communicates this to the investigator in writing, and guides the investigator with the resubmission.

Certain changes might disqualify the activity from its non-human participant or non-research status. Therefore, all changes in the plan that may affect this status must be reported to the IRB for review and verification prior to implementation.

B. Conducting Initial and Continuing Review

The IRB will conduct initial and continuing reviews of human participant research to ensure that all such research is conducted in accordance with the Assurances on file with the DHHS involving human participants, and all other activities that involve such research, regardless of sponsorship. After initial review of applications by the ORP or HSPO for completeness, IRB review of applications is conducted to:

- Determine that the use of human participants has research relevance and to consider ethical issues with regard to the study's design and conduct
- Determine that the proposed research design is scientifically sound and does not unnecessarily expose participants to risks
- Identify the risks associated with the research, as distinguished from the risks of procedures the participants would receive even if not participating in research
- Identify the risk level

- Determine that risks are minimized by using procedures consistent with sound research design and which do not unnecessarily expose participants to risk, whenever appropriate, using procedures already being performed on the participants for treatment or diagnostic purposes
- Identify the probable benefits to be gained from the research
- Determine that the risks are reasonable in relation to the anticipated benefits to participants, if any, and the importance of the knowledge likely to result
- Assure that the participant selection is equitable
- Determine that informed consent for the research and authorization for the use of protected health information will be obtained in accordance with the regulations
- Determine intervals of periodic review
- Determine that adequate provisions are in place for data and safety monitoring, whenever the research involves more than minimal risk
- Determine the adequacy of the provisions to protect the privacy of participants and to maintain the confidentiality of the data
- Where some or all of the participants are likely to be vulnerable, determine that appropriate additional safeguards are in place to protect the rights and welfare of these participants
- Determine that the research meets all current regulatory and institutional requirements

C. Acting as the HIPAA Privacy Board for Research

The IRB will conduct initial and continuing review of all research involving human participants, and all other activities that involve such research, to ensure compliance with 45 CFR 160 and 164 as these regulations relate to the conduct of human participant research under the covered entities within PSU. The IRB acts to:

- Determine that the language for the authorization for the use and disclosure of protected health information (PHI) is complete and consistent with the federal regulations
- Review requests for the waiver of authorization for the use of PHI
- Review requests for the use of PHI of decedents
- Review requests for the review of PHI preparatory to research
- Review requests for the use of a limited data set/data use agreement without a written authorization for the use of PHI
- Review requests for the use of a business associates agreement for research

D. Reporting Findings and Actions to the Investigator and Institution

At COM and UP, IRB findings and actions are reported in writing to the investigator submitting the application. The IRB provides reports to institutional officials on a routine basis and, at any time, upon request. For additional information, see Section X.D.

At UP, all communication with the investigator is done via email. Once final approval is granted, approval notification is sent via email with a formal approval letter on PSU stationary included as an attachment. All correspondence is sent to the PI, advisor, if applicable, co-investigators, and project coordinators.

E. Determining Which Studies Require Review More Often Than Annually

Each expedited and full review study is required to undergo continuing review at a minimum of once every 365 days. At the time of initial approval, or any time thereafter, the IRB may require that a study undergo continuing review at more frequent intervals. For additional information, see Section XI.N.

F. Determining Which Studies Need Verification From Other Sources
Ordinarily, the IRB places trust in the PI of an approved research study to carry out the research as planned and presented to the IRB. However, certain situations may be encountered that would cause the IRB to require verification of information related to the conduct of the study from sources other than the investigators. Examples of such situations would include allegations of misconduct by an investigator, complaints from a participant or a third party "whistle-blower," or a random post-approval review by IRB staff.

G. Determining That No Material Changes Have Occurred Since Previous IRB Review and Approval
As part of the continuing review reporting process, the PI must specify what changes, if any, have occurred since the previous IRB review. IRB staff may perform a post-approval review of any study's records to ascertain the degree of compliance.

H. Insuring That Changes in Approved Research Are Not Initiated Without IRB Review and Approval
As outlined in approval letters, investigators agree to notify the ORP/HSPO of any proposed changes to the research study. All investigators are required to submit any changes to the research study to the IRB for review and approval before implementation, except where necessary to eliminate apparent immediate hazards to the participants. Changes include, but are not limited to, the following: (1) procedures involving human participants; (2) informed consent form or informed consent procedures; and (3) identity of the investigators and/or personnel involved in the study. In the case of changes implemented to eliminate immediate hazards to the participant, the IRB must be notified according to the reporting requirements explained in the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others". To insure compliance, IRB staff may conduct random post-approval reviews. Continuing education efforts are made to ensure that investigators understand the need for compliance with this requirement.

I. Insuring Prompt Reporting of Unanticipated Problems Involving Risks to Participants or Others to the IRB
All investigators are required to report to the ORP/HSPO, promptly, the problems listed in the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others". For additional information, see Sections IX.I., IX.J, and X.G.

J. Suspension or Termination of IRB Approved Research
It is the policy of the IRB that the approval status of all currently approved research is subject to suspension or termination, as deemed necessary by the IRB. The IRB may suspend or terminate research that is not being conducted in accordance with the IRB's requirements or the Federal regulations, or if it has been associated with unexpected serious harm to participants.

A suspension for cause is an action initiated by the IRB to temporarily stop some or all research procedures pending further action by the IRB or by the investigator or his/her study personnel. Termination for cause is an action initiated by the IRB to permanently stop some or all research procedures. Examples of a suspension or termination for cause might include: (1) inappropriate involvement of human participants in research; (2) inhibition of the rights or welfare of participants; (3) serious or continuing non-compliance with Federal regulations or IRB policies; or (4) new information regarding increased risk to human participants. This may occur through a complaint received by the IRB, an allegation of non-compliance to the IRB, a discovery by the investigator of potential additional risks, or IRB deliberations. In addition, if concerns are not associated with a specific study, but are investigator

specific, the IRB determines if requesting suspension or termination for cause on other studies under the direction of that investigator is warranted.

The IRB reviews a study for suspension or termination for cause at a convened IRB meeting. Examples of the circumstances warranting such action include:

- Falsification of study safety data;
- Failure by the investigator to place requested activities on suspension when requested by the sponsor;
- Repeated or deliberate failure to obtain or document informed consent from human participants;
- Repeated or deliberate failure to limit administration of the investigational drug or device to those participants under the investigator's supervision;
- Repeated or deliberate failure to comply with conditions placed on the study by the institution, IRB, sponsor or FDA;
- Repeated or deliberate failure to obtain prior review and approval of new studies and continuing review of on-going human participant research by the IRB;
- Repeated or deliberate failure to comply with the approved study, e.g., by enrolling participants who should have been excluded because of concomitant illnesses that put those participants at greater risk;
- Repeated or deliberate failure to maintain accurate study records or submit required problem reports to the IRB;
- Repeated or deliberate falsification or concealment of study records, e.g., by substituting in study records the results of biological samples from participants who met the inclusion criteria for samples of participants who did not meet the inclusion criteria, or by fabricating participants;
- New information regarding increased risk to human participants; and/or
- Inconsistencies in the study and supporting documents for previously approved research.

An IRB Chair or the ORP or HSPO Director may determine if immediate suspension of study procedures and/or study enrollment is required for the study in question, as well as for other studies under the same investigator. This initial decision is based on a preliminary review of available information, communication with the principal investigator(s) involved in alleged non-compliance activities, and the seriousness of the allegations. (See the IRB SOP Addendum "Handling Allegations of Non-compliance") A report of an emergency suspension will be reported and reviewed at the next applicable convened IRB meeting, i.e., for COM, the next board meeting and for UP, at the next Biomedical or Social Science Board meeting, as applicable.

Prior to the presentation of the suspension or termination for cause to the convened IRB, Senior IRB Administration consult with one another in order to organize a presentation of the facts for consideration and vote at the next IRB meeting. The IRB may request an ad hoc review from an independent source with expertise in the type of research being conducted or in the specific area of concern.

Suspensions may include: (1) suspension to recruitment; (2) suspension to screening/enrollment; (3) suspension to interaction/intervention; and/or (4) suspension to follow-up. For all suspensions and terminations, the principal investigator is contacted within one working day by Senior IRB Administrations to inform him/her of the IRB decision. In addition, the IRB notifies the principal investigator in writing, of its decision to suspend or terminate the study for cause and provides a rationale for its actions. This letter includes an opportunity for the principal investigator to respond to the IRB's

determinations and to attend an IRB meeting to discuss the suspension or termination and provide clarification of the issues. In addition, the letter to the principal investigator requires him/her to submit to the IRB proposed procedures for withdrawal of currently enrolled participants that considers their rights and welfare and a proposed script or letter notifying all currently enrolled participants of the suspension or termination. The IRB needs to consider if there are currently enrolled participants in the study and if these participants will be harmed by stopping the study. If there is the potential for harm by stopping the study, the IRB may take the following actions:

1. Transfer the participants to another investigator conducting the same study.
2. Have another investigator take over as PI and keep the participants in the study.
3. Arrange for medical care outside the research.
4. Continue participants in the protocol under the current investigator with additional protections, such as close monitoring or supervision.

If participant follow-up for safety reasons is permitted/required by the IRB, participants should be so informed. The IRB may directly contact participants to fulfill this notification.

Principal investigators are also required to report any problems or outcomes to the IRB or sponsor that would have required reporting if the study had not been suspended.

The IRB may mandate oversight or transfer responsibility to another investigator to ensure implementation of these procedures. The IRB reviews and approves the proposed procedures, scripts or letters prior to implementation.

For a suspension for cause, the IRB may request the development of an education plan or a directed on-site review. Research suspended for cause may be reinstated for approval after corrective actions are completed to the IRB's satisfaction. The IRB may approve the study with or without additional restrictions (e.g., mandating a data and safety monitoring board to oversee the research at designated intervals, increase in the frequency of IRB review or observation of the consent process).

A sponsor-imposed suspension is a determination by the sponsor of the study to place specific research activities on hold. This determination may be made for interim data analysis; inadequate drug availability; response to a data safety monitoring board recommendation; or a pre-planned stopping point. If the suspension is not a planned part of the approved research study, the investigator reports a sponsor-imposed suspension to the IRB as a problem requiring prompt reporting according to the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others". Investigators forward any correspondence from the sponsor, indicating suspension or removal of suspension. Research activities cease as specified in the suspension imposed by the sponsor until the study is re-opened by the sponsor and the IRB. Suspension or reinstatement of research by a sponsor for issues unrelated to risk is considered a minor modification and may be reviewed by the expedited procedure. Sponsor-imposed suspension and reinstatement of research that is related to risk is reviewed and approved by the convened IRB and evaluated as a potential unanticipated problem involving risk to participants or others and as a modification to previously approved research. The IRB may impose additional restrictions upon research conducted under its jurisdiction. The IRB notifies the investigator in writing of its determinations.

All suspensions and terminations will be reported according to IRB policy (See Section IX.J.)

K. Reporting of Unanticipated Problems, Terminations, Suspensions, and Non-compliance

Definitions regarding unanticipated problems, non-compliance, terminations and suspensions may be found in the IRB SOP Procedure Addendum "Handling Allegations of Non-compliance" as well as the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others".

It is the responsibility of the IRB to assure reporting occurs according to the Federal regulations, institutional policy and IRB policy. The IRB will maintain written procedures for assuring prompt reporting to the IRB, appropriate institutional officials and the Federal Department or Agency head, if applicable, of any unanticipated problems involving risk to participants or others, any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB, and any suspension and termination of IRB approval for any reason. This reporting will take place within 30 days of the completion of an investigation and/or determination. The IRB staff prepare a letter that outlines the nature of the event, the findings of the organization and IRB, actions taken by the organization or IRB, reasons for the organization's or IRB's actions, and plans for continued investigation or action. The letter is forwarded to Senior IRB Administration for review and approval. The letter is signed by a member of the Senior IRB Administration. A copy of the letter is sent to:

- IRB members of the applicable committee as an information item in the agenda packet;
- The Institutional Official;
- The Dean of the appropriate College;
- OHRP, if the research is federally funded;
- FDA, if the research is subject to FDA regulation;
- Other "Common Rule Signatories" that may also require reporting if applicable;
- Study sponsor, if the research was sponsored (this includes NIH, NSF, and industry sponsors);
- The HMC Investigational Drug Service, if the research involves investigational drugs, if applicable;
- The Office of Sponsored Programs or the Office of Research Affairs, if the research involves a grant or contract;
- The University Department Chair or Supervisor of the Principal Investigator, if applicable;
- Institutional Officials at external sites where the research is conducted and PSU serves as their IRB of record;
- Legal Counsel, if appropriate;
- Risk Management, if appropriate;
- Clinical Trials Office, if appropriate;
- The General Clinical Research Office, if appropriate; and/or
- Financial Services, if appropriate.

For unanticipated problems involving risks to participants or others, a copy of this letter is not sent to federal agencies if they have already been made aware of the event through other mechanisms, such as reporting by the investigator, sponsor, or another organization.

L. Insuring Through Observation that the Consent Process Includes All Necessary Elements for Informed Consent

Ordinarily, the IRB places trust in the investigators of an approved research study to carry out the consent process as planned and presented to the IRB. However, certain situations may be encountered that would cause the IRB to require verification that all necessary elements in the consent process are present and

adequate. Examples of such situations would include studies where undue influence or coercion of potential participants may easily occur, where the protection for special populations with less autonomy may be questioned, or when continuing review or random post-approval monitoring identifies concerns about the consent process. The convened IRB or Senior IRB Administration may direct an IRB member or a professional staff member from the ORP or HSPO acting on behalf of the IRB to observe and evaluate the elements of the consent process.

X. OPERATIONS OF THE IRB

A. Initial Applications

Submission of New Applications

PSU provides application forms for new studies upon request or through their websites. All applications submitted for IRB review are screened in the ORP or HSPO for completeness before determining the appropriate review level. A complete submission for IRB review includes the following, when applicable: (1) application form; (2) investigator-written or sponsor-provided protocol; (3) informed consent document(s); (4) recruitment materials to include ads, flyers, phone screening procedures, scripts, and/or screening questions; (5) measures that will be utilized: questionnaires, surveys, interview questions, focus group topics, stimuli, etc., that will be used in the study; (6) scientific evaluation, if any; (7) DHHS approved protocol, if any; (8) DHHS approved or sponsor-provided sample consent document, if any; and (9) other materials specific to the proposed study (e.g., grant application, investigator's brochure, sponsor correspondence with a regulatory agency such as the FDA regarding test item, documentation of the IND number or IDE approval letter from the FDA, device information, external safety reports, responses from other committees, pharmacy or device storage and dispensing plan, etc.). If an outside agency, company, clinic, or school is giving the investigator access to its clients, files, or premises, a letter of agreement from that agency that confirms knowledge of the study's purpose and permission for the investigator to conduct the study there.

If the application is incomplete or poorly prepared for review, it is returned to the principal investigator with a request for necessary changes or additional information. IRB staff may contact the investigator by telephone or letter requesting clarification of study issues prior to IRB review. Once a complete application and supporting documents are received, it is assigned an IRB number that remains with the study.

Determination of Review Level

A qualified IRB staff member or IRB Chair pre-screens the application to determine whether the study constitutes human participants research and, if so, the level of review (i.e., convened IRB review, expedited review, or exempt). All studies are assigned to convened IRB review unless: (1) criteria for an expedited review (45 CFR 46.110) are met (see Section X.A., *Expedited Review Process*) or (2) criteria for an exemption review (45 CFR 46.101(b)) are met (see Section X.A., *Exempt Review Process*). All studies involving the use of investigational drugs, devices, or biologics for which an Investigational New Drug (IND)/Investigational Device Application (IDE) is required, receive convened IRB review.

Convened IRB Review Process

- Scheduling of Meetings
  - University Park IRBs:
    The Social Science and Biomedical IRBs each meet once a month. Meeting dates and submission deadlines are posted on the ORP website. Meetings may be cancelled by the Chair in consultation with IRB staff due to: (1) insufficient studies requiring convened IRB review; (2) an inability to secure a quorum for attendance; or (3) other reasons that may arise that make a scheduled meeting unnecessary or otherwise inappropriate. Additional meetings may be scheduled or meetings may be rescheduled as necessary.

  - College of Medicine IRBs:
    Three of the COM IRBs (Boards A, B and C) are each scheduled to meet once a month. The Urgent Issue IRB (Board D) is convened on an ad hoc basis at the discretion of the HSPO Director to respond to urgent issues that cannot wait for a regular scheduled meeting. The IRB Chair or HPA may schedule additional meetings or re-schedule a meeting as necessary.

- Pre-Review
  An IRB Coordinator, Associate Director or Assistant Director – IRB Operations conducts a pre-review of the application materials using a pre-review checklist. The purpose of the pre-review is to verify that all of the required documents have been submitted and to better prepare the application for review by the IRB. An IRB Coordinator, Associate Director or Assistant Director – IRB Operations requests any additional documents needed for the review as well as any pre-review changes to application materials. Once the pre-review changes are received from the investigator, the application materials are placed on the agenda for the next board meeting.

- Pre-Meeting Distributions to Members
  The meeting agendas and study materials are prepared and distributed to IRB members approximately 10 to 15 days in advance to allow adequate time for a thorough review process. The agenda indicates: (1) the meeting date, time, and location; (2) new proposals, modifications, continuing reviews, problem reports, and responses to be reviewed; and (3) any other activities to be discussed at the meeting as determined by the IRB staff.

  The IRB members receive documentation for each item listed on the agenda (if documents are applicable). Specifically, IRB members receive: (1) new application forms and supporting materials; (2) the continuing renewal requests and supporting documentation; (3) the modification requests/revisions and supporting documents; (4) problem report information; (5) previous meeting minutes for review and approval; (6) reports of research approved by the expedited review process; and (7) any other materials as determined by the IRB staff.

- Primary, Secondary and Tertiary Reviewers
  One, two or three IRB members serve as reviewers for new studies requiring convened IRB review. IRB staff, as designated by the Chair, assigns reviewers in advance of a convened IRB meeting. The Chair may serve as a reviewer. In selecting the reviewers, consideration is given to the individual's knowledge of the subject area embodied in the proposal, as well as any known conflict of interest (as defined in Section XVIII.B.). Reviewers are asked to confirm that they do not have any conflicting interests with regard to the research. If an IRB Coordinator is assigned to serve as the only reviewer, he or she must be an IRB member and have the appropriate expertise to review the research.

The primary reviewer leads the discussion of the new study application at the IRB meeting. In the absence of the primary reviewer, these roles default to the secondary or tertiary reviewer. If none of the assigned reviewers are present at the meeting, the review of the project is tabled. While assigning reviewers, the IRB staff checks to ensure that at least one of the assigned reviewers has the appropriate scientific expertise to review the project. If all IRB members are assigned as reviewers, the IRB staff checks to ensure that at least one of the IRB members present at the meeting has the appropriate scientific expertise to review the project. If none of the IRB members have the appropriate scientific expertise, the IRB staff arranges for expert consultation. At COM, the primary reviewer may contact the investigator in advance of the board meeting for additional information or clarification.

Assigned reviewers receive and review the following as applicable:

- Completed application and protocol summary abstract, if applicable, with all information provided by the investigator
- The complete grant proposal (i.e., research funding proposal), if applicable
- The study protocol, if the study involves a clinical or therapeutic intervention (e.g., pharmaceutical company protocol, investigator-initiated clinical protocol)
- The Informed Consent Form(s) or a description in the application as to why an Informed Consent Form is not possible or appropriate for the study
- Recruitment materials (including brochures, flyers, advertisements, audio tapes, video tapes, or letters to potential participants, phone script for situations that will involve providing information to potential participants via telephone) that will be used to inform people about the study
- Measures that will be utilized: questionnaires, surveys, interview questions, focus group topics, stimuli, etc., that will be used in the study
- Scientific evaluation, if any
- If an outside agency, company, clinic, or school is giving the investigator access to its clients, files, or premises, a letter of agreement from that agency that confirms knowledge of the study's purpose and permission for the investigator to conduct the study there for COM. At UP, investigators are required to obtain the letter and maintain it for their records. It must be produced upon request.
- For research involving investigational drugs, the Investigator's Brochure(s) and external safety reports not referenced in the Investigator Brochure(s)
- Documentation of the IND/IDE number, if applicable.
- The DHHS-approved sample informed consent document, if applicable
- The complete DHHS-approved protocol, if applicable

All other IRB members receive the documents below. However, they can request access to all materials related to each submitted study by contacting the ORP/HSPO staff.

- Complete application and protocol summary with all information provided by the investigator;
- Informed consent documents;
- The full protocol if investigator written or selected pages of sponsor-provided protocol;
- Recruitment materials, including advertisements intended to be seen or heard by potential participants;

- Instruments (i.e., surveys, questionnaires, interview/focus group topics or questions); and
- Other relevant material as determined by the IRB staff.

Assigned reviewers are expected to conduct an in-depth review of all materials in advance of the meeting using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met, a list of informed consent requirements and then document their review using the applicable reviewer checklist. IRB members who are not assigned reviewers are expected to review the provided materials in advance of the meeting in enough depth to be familiar with the materials and prepared to discuss them at the meeting.

- <u>Voting and Quorum Requirements</u>
  - Quorum Required to Transact Business:
    To transact business, a majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present to conduct a convened IRB meeting. At least one physician member must be present when research activities involving drugs, biologics or devices are being considered. When reviewing research with children, at least one member knowledgeable about or experienced in working with children must be present. Also, when the IRB reviews research involving prisoners, an ex-prisoner or prisoner representative attends as a voting member.

    IRB staff assigned to coordinate the board meeting are responsible to monitor the members present at the meeting to determine that the IRB is appropriately convened and remains so. IRB staff announce if quorum is lost during a meeting. The IRB does not take further votes until the quorum is restored.

    Members may be present in person or audio or audio-visual teleconference. Members present via teleconference are noted as such in the meeting minutes. Such members must receive all pertinent information prior to the meeting and be able to actively and equally participate in all discussions.

    IRB minutes record the quorum and votes for each IRB action and determination. Members recusing themselves due to conflicts of interest may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining). IRB minutes list by study the names of the members recusing themselves from participation due to conflicts..

  - Types of Voting:
    IRB members may cast a vote for or against a motion, or abstain. Voting is conducted by verbal "yea" or "nay" or a show of hands. The official meeting minutes will record, without individual identification, the number of votes to approve, disapprove, no decision or abstain. It is the policy of the IRB to attempt to gain a consensus of the IRB members during the course of the study review before calling for a vote. A majority vote of the members present at the meeting is required for approval.

    Only individuals listed on the official IRB membership roster as voting members may vote. Alternate members may vote only when the regular member for whom they are authorized to replace is not present at the meeting or is attending the meeting but not voting. Under this

circumstance, the alternate member holds the full voting rights in place of the regular member. An alternate may cast only one vote, even if authorized to replace two regular members and both of the latter are absent. Members unable to attend a meeting (and not available via audio or audio-visual teleconference) cannot vote in absentia.

- Types of Motions:
  The IRB will make a motion for each application request (e.g., new study, modification, continuing review) presented to it. All voting members may vote upon studies according to the following types of motions or another motion offered:
  - Approved with no required changes. The research may proceed.
  - Approved with minor changes clearly delineated by the IRB so that the investigator may simply concur with the IRB's stipulations. The research may proceed after a designated IRB member that can include ORP/HSPO staff members, verifies the required changes.
  - Deferred or tabled pending receipt of additional substantive information. The IRB has determined that the application and supporting documents lack sufficient information to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all the requested information.
  - Disapproved. The IRB has determined that the research cannot be conducted as proposed at PSU or COM/PSHMC or by PSU or COM/PSHMC employees or agents.

- Role of Investigator at IRB Meetings
  At COM, when new studies are to be discussed at the meeting, PIs (and study coordinator and advisor, if applicable) may be invited to attend the meeting to discuss their study with the IRB.

  At UP, the PI and advisor (if applicable) are invited to attend the meeting to discuss their study with the IRB. If an investigator is not able to attend the meeting, the IRB will review the study in the PI's absence and proceed with a motion and vote, if requested by the investigator. An investigator and advisor (if applicable) may be required to attend the meeting for other reasons such as modification requests, non-compliance issues, problem reports, etc.

Expedited Review Process

The expedited review process is used in accordance with federal regulations for studies that qualify for expedited review. To undergo initial or continuing review using the expedited procedure, a study must meet all applicability criteria and involve procedures in one or more of the following categories of research. A review checklist is used to determine that all eligibility criteria for expedited review are met.

DHHS categories for expedited review:

1. Research on drugs for which an investigational new drug application is not required or research on medical devices for which a) an investigational device exemption application is not required or b) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick or venipuncture as follows: (a) from healthy, non-pregnant adults, who weigh at least 110 pounds. For these participants, amounts drawn may not exceed 550 ml in an 8 weeks period and no more than 2 times per week; or (b) from other adults and children, considering age, weight, and health of the participants, collection procedure, amount of blood to be collected, and frequency with which it will be collected. For

these participants, the amount drawn may not exceed the lesser of 50 ml or 3 ml/kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at the time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

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

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

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

8. Continuing review of research previously approved by the convened IRB (a) where the research is permanently closed to the enrollment of new participants, and all participants have completed all research-related interventions, and the research remains active only for long-term follow-up of participants; or (b) where no participants have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or an investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

When the IRB considers a request for expedited review, the IRB distinguishes research that is greater than minimal risk from research that is not greater than minimal risk. Federal regulations define *minimal risk* as the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45 CFR 46.102(i)). In addition, expedited review cannot be used where identification of the participants and/or their responses would reasonably place them at risk of criminal or civil liability, or be damaging to the participants' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

The PI may request expedited review of a study when submitting an application, noting on a checklist of the criteria under which expedited review is possible. The IRB Chair or his/her designee take this under consideration, but have the ultimate responsibility for making the decision whether to review through the expedited process, refer to the convened IRB or exempt the study.

For each application undergoing review by the expedited process, the IRB staff, as designated by the Chair, selects one or two qualified reviewers from the list of experienced IRB members to conduct review using the expedited procedure. These reviewers may also request review of the research by an expert consultant for issues that require expertise beyond, or in addition to, that available on the IRB. In selecting the reviewers, consideration is given to the individual's knowledge of the subject area embodied in the proposal, as well as any known conflict of interest (as defined in Section XVIII.B.). Reviewers are asked to confirm that they do not have any conflicting interests with regard to the research.

For initial review of an application using the expedited review process, the reviewers receive all submitted materials, including at a minimum the same materials that would have been provided to a primary reviewer had the research been reviewed by the convened IRB. Assigned reviewers are expected to conduct an in-depth review of all materials using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist.

The IRB Chair or his/her designee may approve studies as submitted or require modifications prior to approval. They are not empowered to disapprove studies reviewed through the expedited process; in such cases, the study must be submitted for convened IRB review along with the comments and recommendations of the chair or his/her designee. Approved expedited studies are subject to at least an annual review. This information is communicated to the principal investigator in the approval letter. Studies reviewed and approved through the expedited process are reported to all IRB members on the IRB meeting agenda. At COM, the IRB members receive a detailed description for all new research approved by the expedited process.

Exempt Review Process

Certain types of research may be found by the ORP/HSPO to be "exempt" from IRB oversight (45 CFR 46.101[b]). Investigators, however, may not make an independent determination that research is "exempt" from the review process. Only a designated IRB member or qualified ORP/HSPO staff has the authority to determine if a research study is "exempt" from IRB oversight. Reviewers are asked to confirm that they do not have any conflicting interests with regard to the research.

For initial exemption determination review, the reviewers receive all of the required forms and documents submitted by the investigator for review. The reviewers are responsible for making determinations of exemption from the requirements of 45 CFR 46 in accordance with 46,101(b)(1-6) as listed below. Research that qualifies for exemption from the requirements must fall within one or more of the six exempt categories:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special educational instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. **(This category *may* include children. This category may NOT include prisoners or be FDA-regulated.)**

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless (a) information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and (b) any disclosure of the human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation. **(This category may NOT include prisoners or be FDA-regulated.**

    - Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) for which participants cannot be identified or release of the information would not be harmful to the participant**(This category *may* include children.)**
    - Research involving the use of survey procedures or interview procedures or observation of public behavior for which participants cannot be identified or release of the information would not be harmful to the participant. **(**When research involves children as subjects this exemption must be limited to educational tests (cognitive, diagnostic, aptitude achievement)and observation of public behavior when the investigators do not participate in the activities being observed. Research that uses survey procedures, interview procedures, or observation of public behavior when the investigators participate in the activities being observed cannot be granted an exemption.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior not otherwise exempt under the above two categories if the human participants are elected or appointed public officials or candidates for public office; or federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. **(This category may NOT include prisoners or be FDA-regulated.)**

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is

recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants. **(This category *may* include children. Existing data means the items exist [are 'on the shelf'] before the research was proposed or were collected prior to the research for any purpose. This category may NOT include prisoners or be FDA-regulated.) Under this exemption, an investigator may inspect identifiable records, but may only record information in a non-identifiable manner.**

5. Research and demonstration studies which are designed to study, evaluate, or otherwise examine public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payments for benefits or services under those programs. **(This category *may* include children. This category may NOT include prisoners or be FDA-regulated.)**

    - The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).
    - The research or demonstration project must be conducted pursuant to specific federal statutory authority.
    - There must be no statutory requirement that an IRB review the project.
    - The project must not involve significant physical invasions or intrusions upon the privacy of participants.
    - The Office for Human Research Protections (OHRP) [or the applicable federal agency] has authorized or concurred with this exemption determination.

6. Taste and food quality evaluation and consumer acceptance studies if wholesome foods without additives are consumed; or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the United States Department of Agriculture (USDA). **(This category *may* include children. This category may NOT include prisoners.)**

Exemptions are not available for the following types of research:

- Research involving prisoners
- Survey or interview research involving children that would fall into category 2
- Observational research of children is not exempt unless the observation of a child's public behavior does not involve participation by the investigator
- Research subject to FDA regulations unless the research falls into category 6

When providing review of exempt research, the reviewers are also responsible for determining that the research meets the institution's ethical principles for human participant research and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Assigned reviewers are expected to conduct an in-depth review of all materials using a reviewer checklist to document review and exemption determinations.

The reviewers may request additional information from the principal investigator to make the determination or request changes in the research to meet the institution's ethical principles for human

participant protection and the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. When the reviewers require additional information or modifications in the research to secure the exemption determination, the ORP/HSPO notifies the principal investigator in writing of the required modifications or additional information required to make the determination. When received, the reviewers review the principal investigator's response and, when applicable, make the exemption determination. The reviewers may continue to request information or require modifications until a determination can be made.

If the reviewers determine that the research is exempt from the requirement of 45 CFR 46, the ORP/HSPO notifies the principal investigator in writing that the research is exempt from further IRB review. If the research does not meet the criteria for exemption, the protocol is reviewed either at a convened meeting of the IRB or using the expedited review procedure, whichever is appropriate to the research activities.

Documentation of verified exemptions will be included in the IRB research study file and will consist of the reviewer's written concurrence that the activity described in the investigator's application for exempt research satisfies the conditions of the cited exemption category. At COM, studies that are determined to be human participant research that are exempt from IRB oversight are reported to the IRB members at the next IRB meeting. At UP, exempt studies are available to IRB members upon request.

At COM, investigators conducting research designated as exempt are required to report any proposed changes in the research activity that may affect the exempt status. At UP, all proposed changes need to be submitted. Review must be obtained before such changes are initiated, except where necessary to eliminate apparent immediate hazards to the participant. Investigators must also report any problems that require prompt reporting according to the "IRB Standard Operating Procedure Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others". Reviewers of exempt research may request additional protections be incorporated into the research study, such as the informed consent process.

If the research is determined to be exempt from the requirements of 45 CFR 46, continuing review is not required. At COM, status reports are received from investigators at 5-year intervals to report on the activity of the exempt research and indicate the study is on-going. At UP, status reports are received from investigators at 3-year intervals to report on the activity of the exempt research and indicate the study is on-going.

Length of Approval

For expedited and convened IRB studies, approval is granted for a maximum of one year. Approval periods requiring more frequent review may be designated, when appropriate. For additional information, see Section XI.N. For research reviewed by the convened IRB, the expiration date is defined as the first day on which the project is no longer approved. At UP, it is calculated by adding the interval of approval to the date of the convened meeting at which the IRB reviewed and approved the study. At COM, it is calculated by adding the interval of approval to the date of the convened meeting at which the IRB reviewed and approved the study, then backtracking to the final day of the last whole month of the approval period. Continuing review must occur, at a minimum, within 365 days of the convened IRB meeting date at which the IRB reviewed and approved the study. If the IRB determines that a shorter interval is needed, the expiration date can be changed to reflect that stipulation. For research reviewed at the expedited level, continuing review must occur within 365 days of the date the reviewer approved the study.

Upon final approval of a new application, the ORP/HSPO stamps the informed consent form(s) with the approval and/or expiration dates. These documents are sent to the principal investigator. In addition, the investigator receives a memo indicating type of review, approval and expiration dates, and a summary of principal investigator responsibilities. At UP, a copy of the approval memo is also sent to the co-investigator(s), project coordinator, and advisor, if applicable.

B. Continuing Reviews

When a research study is due for continuing review, an email and a Continuing Progress Report (CPR) form are sent to the principal investigator and/or designated contact person via PSU's Protocol Review and Approval Management System (PRAMS) 75 days before the approval expiration date. At UP, co-investigators, project coordinators, and advisors, if applicable, receive a copy of the email notification. If the CPR has not been received within 45 days of the approval expiration date, another email reminder and CPR form are sent automatically.

Continuing review must be substantive and meaningful. If necessary, the research study should be revised to meet current regulatory and institutional requirements. The approval criteria for continuing review are the same as that for initial review. (See Section XI.) Investigators are required to submit the following documents for continuing review for all expedited and convened IRB studies:

- A completed CPR which provides a status report on the progress of the research, including a summary of enrollment, withdrawals, adverse events and problems that required prompt reporting, other internal problems that were expected and related to the research, and any other relevant information;
- Any data safety monitoring reports;
- Any reports or publications resulting from or relevant to the research;
- Any correspondence with the Food and Drug Administration;
- Any reports from auditors;
- The current, approved consent documents;
- The current, approved recruitment materials; and
- At the request of the IRB initial reviewer, if needed to fulfill the approval criteria for continuing review, a newly proposed consent document.

Modifications to a research study are not to be submitted during the continuation review process unless they are necessary to fulfill approval criteria.

When a CPR form is received, the packet is checked for completeness, logged in, and given to a designated IRB member for review and determination of the review level. The reviewer uses a continuation review checklist to determine eligibility for expedited continuing review. To undergo continuing review using the expedited process, a protocol must meet all applicability criteria and involve procedures in one or more categories of research listed in Section X.A.

For research studies requiring continuing review by the convened IRB, the review is scheduled for an IRB meeting held within 30 days of the approval expiration date. Two reviewers are assigned for continuing reviews that require convened IRB review. One reviewer is an in-office, IRB-member who has access to the complete IRB study file and reviews the study including but not limited to any modifications previously approved by the IRB, CPR, consent form, problem reports, any complaints, and any relevant communications from the sponsor. The other reviewer, the primary reviewer, is an IRB member who is not an IRB staff member. The primary reviewer and all other IRB members receive the following

information prior to the IRB meeting: (1) the completed CPR; (2) protocol summary if applicable; (3) most recently approved consent form(s); (4) a newly proposed consent form, if needed to fulfill the approval criteria; (5) most recently approved recruitment materials; (6) the sponsor's or investigator-written protocol; and (7) any other materials containing the relevant information to determine whether the proposed research continues to fulfill the criteria for approval. This material is provided to all IRB members either electronically or as part of the agenda packet distributed before the meeting. The assigned reviewers conduct an in-depth review of all materials in advance of the meeting using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist. All other IRB members review the provided materials in advance of the meeting in enough depth to be familiar with the materials and prepared to discuss them at the meeting. Prior to and during the IRB meetings, the IRB members may obtain protocol files and IRB meeting minutes from the HSPO/ORP staff. At the meeting one of the reviewers summarizes the activity and progress of the study for the IRB, initiates the discussion of the research, and makes a recommendation about continuing approval following the discussion. The Chair and the reviewers are responsible for making sure that all regulatory criteria are addressed and that a substantive discussion occurs. The IRB votes on each study using the motions described in Section X.A.,

Convened IRB Review Process.
For studies that qualify for expedited review, the review is completed within 30 days of the approval expiration date. For each study undergoing continuing review by the expedited review process, the IRB staff selects a qualified reviewer from the list of experienced IRB members designated by the Chair to conduct review using the expedited procedure. The reviewer is provided all submitted materials, including at a minimum the same materials that would have been provided to the primary reviewer had the research been reviewed by a convened IRB. Assigned reviewers are expected to conduct an in-depth review of all materials using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist.

Studies that receive continuing approval through the expedited review process are reported to IRB members on a convened IRB meeting agenda.

Continuing IRB review of studies must occur as long as the research remains active for long-term follow-up of participants, even when the research is permanently closed to the enrollment of new participants and all participants have completed all research procedures. In addition, as long as a non-exempt human participant research project continues to involve analysis of individually identifiable private information by the investigator, the research continues to involve human participants and must undergo continuing review by an IRB at least annually. In accordance with Federal regulations, the continuing review of a study must also occur even when the remaining research activities are limited to data analysis.

Principal investigators and advisors (if PI is a student) are notified in writing of the decision of the IRB and any requested changes. The IRB may grant renewed approval with changes when the changes are clearly delineated by the IRB so that the investigator can simply concur with the IRB's stipulations. The research may proceed after a designated IRB member verifies the required changes. Upon final approval, the ORP/HSPO stamps the informed consent form(s) with the approval and/or expiration dates. These documents are sent to the principal investigator. In addition, the investigator receives a memo indicating type of review, approval expiration date, and a summary of principal investigator responsibilities. At UP,

a copy of the approval memo is also sent to the co-investigator(s), project coordinator, and advisor, if applicable.

At UP, if, after five years of IRB approval for a given study, a PI requests continuation, he/she must submit a continuing progress report and a new application form along with all documents that are requested for an initial application process.

If an investigator fails to provide the continuing review information prior to the expiration date or the IRB has not reviewed and approved the research study by the expiration date specified by the IRB, the principal investigator is notified in writing that enrollment of new participants and all research activities must stop and that any continuation or research activity is a violation of Federal regulations. The letter also indicates that the investigator must immediately notify the IRB in writing if there is an over-riding safety concern or ethical issue involved such that it is in the best interests of individual participants to continue participating in study interventions or interactions. The IRB Chair and/or the ORP/HSPO Director determine which individuals may continue in the research study. Reinstatement of the research requires submission of a research application and supporting materials for initial review.

C. Modifications

Investigators must report planned changes in a study and receive approval from the IRB prior to implementing these changes, except where necessary to eliminate apparent immediate hazards to the participants. In the case of changes implemented to eliminate immediate hazards to the participants, the emergency protocol deviation must be reported according to the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others".

When a principal investigator wishes to modify a study, he or she must submit these modifications to the IRB along with any supporting documentation. Modifications may include, but are not limited to:

- changes to a study
- adding or removing investigators/study personnel
- requesting additional participants beyond the approved number
- changes in funding
- changes in informed consent process or form(s)

Federal and FDA regulations permit an IRB to review research modifications to convened review studies through an expedited procedure if the research constitutes a minor change in previously approved research during the period for which approval is authorized. Minor changes include those that: (1) do not change the risk/benefit ratio to a participant; (2) would not change the IRB's conditions for approval; and (3) would not impact a participant's decision to remain in the research. An IRB Chair and/or his/her designee determines the review level of a modification for an ongoing study based on the amount of risk to the research participant. For additional information, see the "Guidance for Substantive vs. Minor Changes in Research" document.

The IRB Chair or his/her designee may review the following types of revisions through an expedited procedure:

- Informational revisions with no potential impact on the risks for participants, (e.g., editorial changes, changes to research staff, reduction in the number of research participants, or deletion of questions on questionnaires)

- Minor revisions with minimal risk to the research participant, (e.g., increasing the number of participants, adding non-sensitive questions to a questionnaire, adding a standardized test, changing the recruitment plan or recruitment materials, adding a standard quality-of-life questionnaire, extending the time period of the study to include only follow-up with the research participants, changes to the research staff members, adding a research site, revising the format of the consent form, changing telephone numbers or contact persons on the consent forms, minor changes to participant compensation, or other minor revisions to the consent forms). See "Guidance for Determining Substantive vs. Minor Changes in Research".

For revisions undergoing review by the expedited process, the IRB staff selects a qualified reviewer from the list of experienced IRB members designated by the Chair to conduct review using the expedited procedure. The IRB member responsible for the expedited review is provided all submitted materials including at a minimum the same materials that would have been provided to the primary reviewer had the research been reviewed by a convened IRB. The reviewers evaluate if the modification is a minor change to previously approved research and conduct an in-depth review of all materials using a reviewer checklist. The reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist. The reviewers may approve modifications as submitted or require changes prior to approval. They are not empowered to disapprove modifications reviewed through the expedited process. In such cases, the modification must be submitted for convened IRB review along with the comments and recommendations of the reviewer. Study modifications that receive approval through the expedited review process are reported to all IRB members on the next IRB meeting agenda.

All other changes must be reviewed and approved by the convened IRB. This type of modification reflects a major change in the direction of the study that may substantially change the purpose/goals of the study or may affect a participant's decision to remain in the research. Examples of such changes with major risks include: changes in the treatment or drug dosage or frequency, additions or deletions of research groups, revisions to eligibility criteria, or changes to the consent form to include newly identified side effects or adverse events.

At COM, two reviewers are assigned for modifications that require convened IRB review. One reviewer is an in-office IRB member who has access to the complete IRB study file. The other reviewer, the primary reviewer, is an IRB member who is not an IRB staff member. The primary reviewer and all other IRB members receive a copy of the study modification, the protocol summary, consent form, and any other relevant communications from the sponsor or investigator as part of the agenda packet distributed before the meeting at which the modification review is scheduled. The assigned reviewers conduct an in-depth review of all materials in advance of the meeting using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist. All other IRB members review the provided materials in advance of the meeting in enough depth to be familiar with the materials and prepared to discuss them at the meeting. Prior to and during the IRB meetings, the IRB members may obtain protocol files and IRB meeting minutes from the HSPO staff. At the meeting, the primary reviewer summarizes the modification, initiates the discussion, and makes a recommendation about the modification following the discussion. The Chair and the reviewers are responsible for making sure that all regulatory criteria are addressed and that a

substantive discussion occurs. The IRB votes on each study modification using the motions described in Section X.A., *Convened IRB Review Process*.

At UP, two reviewers are assigned for modification reviews that require convened IRB review. An ORP staff member who is also an IRB member serves as primary reviewer. This individual reviews the complete IRB study file, including but not limited to any modifications previously approved by the IRB, consent form, problem reports, any complaints, and any relevant communications from the sponsor. A secondary reviewer, who is not an ORP staff member, is assigned from IRB members attending the meeting. If the expertise of a physician or other expert is needed, an MD or other expert is assigned as the secondary reviewer. The secondary reviewer and all other IRB members receive the following information prior to the IRB meeting: (1) the completed modification request form; (2) most recently approved consent form(s) if applicable; (3) a newly proposed consent form if needed to fulfill the approval criteria if applicable; and (4) any other materials containing the relevant information to determine whether the proposed research continues to fulfill the criteria for approval. The assigned reviewers conduct an in-depth review of all materials in advance of the meeting using a reviewer checklist. Reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of the regulatory criteria that must be met and a list of informed consent requirements and then document their review using the applicable reviewer checklist. All other IRB members review the provided materials in advance of the meeting in enough depth to be familiar with the materials and prepared to discuss them at the meeting. Prior to and during the IRB meetings, the IRB members may obtain protocol files and IRB meeting minutes from ORP staff. At the meeting the primary reviewer summarizes the modification for the IRB and initiates the discussion of the research. The Chair and the reviewers are responsible for making sure that all regulatory criteria are addressed and that a substantive discussion occurs. The IRB votes on each study modification using the motions described in Section X.A., *Convened IRB Review Process*.

Modifications may require the consent form/process be revised to reflect study changes. Investigators must submit a revised consent form for new (not yet enrolled) participants and a consent form addendum to provide the new information to current (already enrolled) participants, if applicable.

The IRB may grant approval with changes when the changes are clearly delineated by the IRB so that the investigator can simply concur with the IRB's stipulations. The research may proceed after a designated IRB member verifies the required changes. Upon final approval, if the modification includes revisions to the informed consent document, the ORP/HSPO stamps the informed consent form(s) with the date of approval and/or the date of expiration. The forms are sent to the principal investigator along with a memo indicating type of review, approval expiration date, and a summary of responsibilities.

D. Communication from the IRB

To the Investigator Conveying the IRB's Decision

The IRB will notify the investigator in writing of its decision to approve or disapprove the proposed research study, or of modifications required to secure IRB approval of the research study within 7-10 business days of the IRB completing its review.

At COM, notification that involves the results of a convened IRB meeting includes the minutes of that meeting.

At UP, all communication with the investigator is done electronically. Once final approval occurs, approval is sent via email with the formal approval letter on PSU stationary included as an attachment. Communications are sent to the PI, advisor, if applicable, co-investigators, and project coordinators.

To the Institution's Administration Conveying the IRB's Decision
At UP, approval and approval expiration reports are sent to department heads and research deans of each college/unit upon request. Reports are also provided to the Institutional Official at her request. At COM, a copy of the IRB minutes are sent on a monthly basis to the Institutional Official.

To the Sponsor of Research Conveying the IRB's Decision
The PI is responsible for notifying the sponsor concerning IRB decisions. Assistance in notifying sponsors is available, when requested.

E. Revisions Prior to Final Approval
Revisions to new and continuing human participant applications may be required. Correspondence is sent to the principal investigator, advisor, if the PI is a student, and project coordinator, if applicable, detailing requests for revisions, clarification, or additional information. The principal investigator is expected to address the requested revisions within a given and stated timeframe, generally 30 to 90 days.

If a response is not received within the stated timeframe, a reminder is sent to the principal investigator to respond to the request. If no response is received, the study or proposed modification is withdrawn from consideration. If the principal investigator wishes to conduct a study that has been withdrawn from consideration, he/she must submit a new application or modification request for IRB review and approval.

When specific changes are requested in the application and/or supporting document(s), the responses are reviewed for compliance. When the IRB designates a reviewer to confirm that the final requirements are addressed, the study receives final approval when all required changes have been submitted and approved.

Upon final approval, an approval stamp is placed on the informed consent document(s) that indicates the dates of approval and/or approval expiration. In addition, the principal investigator receives a memo indicating the type of review, approval expiration date and a summary of investigator responsibilities. The memo informs the investigators of their responsibility to notify the ORP/HSPO of any additions or changes to the study. All investigators are required to submit any changes to the research study to the IRB for review and approval before implementation, except where necessary to eliminate apparent immediate hazards to the participants. See Section X.C. for additional information.

F. Rebuttal or Appeal of IRB Decisions
Upon receipt of requested changes, investigators may appeal the IRB recommendations either in person or in writing. If the IRB decides to disapprove a research activity, written notification including a statement of reasons for its decision will be provided to the investigator. An appeal of a disapproved research study must be reviewed at a convened IRB meeting. The response and study are reviewed by the IRB that made the original decision. Additional appeals to the IRB may be made by the principal investigator.

G. Unanticipated Problems Involving Risks to Participants or Others
Reports of problems that require prompt reporting to the IRB are reviewed according to the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others"**.** The IRB, the IRB Chair, and the ORP/HSPO Directors have the authority to suspend or terminate

approval of human participant research if the unanticipated problem increases the risk level to participants. See Section IX.J. for additional information.

H. Post IRB Approval Review

The IRB reviews and assesses approved research to assure human participant protection remains prominent in the foundation of the research. On-site post IRB approval review is conducted at the discretion of the IRB for routine, directed and for cause reviews. Either an IRB member or a professional ORP/HSPO staff member acting on behalf of the IRB conducts the review visit. The IRB may engage an external consultant with a specific area of expertise to perform or assist with the review activities. Periodic routine post approval reviews may include a random selection of research studies meeting exempt, expedited, and convened IRB reviews. In addition, studies involving an investigator-held IND or IDE may be reviewed to evaluate the investigator's knowledge about the additional regulatory requirements of sponsors and to assess compliance with these requirements. A directed or for cause on-site review may occur when a concern (e.g. a continuing review of a study or report from other sources indicates that changes have occurred without prior IRB approval, investigators have failed to comply with IRB policies and procedures, potential problem areas are identified due to investigator inexperience, new procedures, etc.) is identified by a convened IRB, an external agency, a sponsor, a study participant, or institutional personnel.

The review process assesses adherence to Federal regulations, IRB policies and procedures, the study protocol, accurate documentation and reporting of study-related activities, and evaluation of the informed consent process. The review process may also be an educational activity.

The review process may include, but is not limited to the following:

1. Discussions with investigators and other study personnel to ascertain their level of knowledge of the guiding principles and policies of the IRB
2. Observation and/or discussion of the recruitment or consent process
3. Examination of some or all signed informed consent forms
4. Observation of the research activity
5. Interviews with screened or enrolled participants
6. Examination of research records
7. Requests for progress reports and problem reports from investigators
8. Educational instruction for study investigators and study personnel

The review procedures may incorporate the following:

- The investigator is notified by letter to set up a date and time for a review. The visit time and place is confirmed 24-48 hours prior to the visit.
- The reviewer uses the necessary current documents from the IRB study file.
- The reviewer analyzes the study for conduct and documentation according to the approved study protocol, IRB policies and procedures, and federal regulations.
- A written report of the post approval review activity is sent to the investigator. A copy is maintained in the ORP/HSPO.
- Discussion with the study team members to ascertain the quality of interactions with the IRB and/or ORP/HSPO and familiarity with specific study procedures.

Follow-up to the review may include the following:

- If the report determines that all procedures are in compliance, the report is filed at the ORP/HSPO and a letter indicating such is sent to the principal investigator.
- If the report determines there are minor infractions or inconsistencies with the approved study or with IRB policies and procedures and there is no or minimal increase in risk to participants, a letter is sent to the principal investigator outlining the problem areas and requesting these areas be addressed.
- If non-compliance is suspected, the IRB SOP Addendum, "Handling of Allegations of Non-compliance" is implemented immediately.

Quality improvement will be implemented as needed. Additional guidelines and/or education will be developed when necessary. Periodic internal assessments of the IRB/HSPO/ORP cross-reference issues shared by researchers with the institutional policies and procedures, evaluating the system for areas where communications and process can be improved.

A post IRB approval review may involve a thorough review of the recruitment and/or informed consent process. This includes: (1) a review of the number of consent forms signed to assess consistency with the number of participants enrolled; (2) confirmation of the use of the most currently approved form; (3) a review of the signed consent forms for all necessary signatures and dates; (4) a review, including observation if appropriate, of the process of obtaining informed consent with a research participant; and (5) a review of the recruitment process and recruitment documents.

I. Complaints Regarding Human Participant Research

The ORP and HSPO provide information concerning methods to offer complaints about human participant research or the human research protection program. This information is provided on the IRB websites, brochures and informed consent forms. Persons who want to address a complaint to someone outside of the IRBs and HSPO/ORP may contact the Senior Vice President for Research at University Park or the Vice Dean for Research at the College of Medicine.

It is IRB policy to investigate all complaints received regarding human participant research conducted under its jurisdiction. The Senior Vice President for Research, the Vice Dean for Research, and Senior IRB Administration will investigate all complaints received regarding research under the PSU IRB's jurisdiction. The level of investigation will depend on the seriousness of the situation and the potential risk to participants. Complaints may come from any source including IRB members, investigators, participants and their families, institutional personnel, other institutional committees, the media, anonymous sources or the public. Complaints may come from any category of research reviewed and may include anyone involved or not directly involved in the research study. The investigation will result in finding a suitable resolution and response to the complainant in a timely manner. All complaints will be handled in a confidential manner. This includes any individual involved in notifying the PSU IRB of an alleged violation of investigator compliance (e.g., whistle-blower). Complaints that are substantiated will be further investigated through an audit conducted by the ORP/HSPO. Additional actions will be taken as deemed appropriate by the IRB. If non-compliance is suspected, the IRB SOP Addendum "Handling Allegations of Non-compliance" is followed.

It is the responsibility of the principal investigator to (1) notify the IRB of any participant or other individual's complaint regarding the research and (2) report complaints that involve potential risks to participants/others or result in a potential change in the risk/benefit ratio as a reportable problem (e.g., the school where the research is conducted complains that the research assistant has not maintained her research notes in a confidential manner which may have potentially breached confidentiality) according to

the “IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others”. The complaint may be reported at continuing review if it involves no risk to the participants or others or does not change the risk/benefit ratio (e.g., a participant complains that he/she does not like the investigator’s clinic hours and subsequently withdraws from the study). Investigators are to cooperate with the IRB by making documents accessible, responding to written requests within the designated timeframe, and being available for questions by the IRB.

When a complaint is received by a member of the human research protection program, he/she collects as much detail as possible and Senior IRB Administration is notified. When a complaint is substantiated, Senior IRB Administration assigns an IRB Coordinator to conduct an investigation. The results of the investigation will be reported to the Senior IRB Administration. These individuals may request revisions or additions to the planned investigation or audit activities. At the completion of the investigation or audit, the findings, if warranted, will be taken to the appropriate convened IRB for review. A determination will be made by the IRB if any further actions that are to be taken.

J. Non-compliance Investigations and Actions

Under institutional authority and federal regulations [Title 45 CFR 46.103(b)(5), Title 45 CFR 46.113, Title 21 CFR 56.113], IRBs are responsible to oversee the safety of research participants and may suspend or terminate human participant research that is not being conducted in accordance with federal and institutional requirements. The IRBs are supported in this process by the ORP and/or the HSPO. For specific information as to how allegations of non-compliance are handled by the IRBs, please see the “IRB SOP Addendum: Handling of Allegations of Non-compliance”.

K. Monitoring the Use of Protected Health Information (PHI)

Review of Requests for Use of PHI of Decedents

The HIPAA Privacy Rule protects the protected health information (PHI) of persons who have died. Because it may be necessary for a researcher to obtain access to and review the PHI of decedents, Title 45 CFR 164.512(i)(1)(iii) allows such review upon compliance with specified criteria. As the designated Privacy Boards for research at PSU, the IRBs have the authority to review and approve requests for the use of PHI of decedents. The IRB Chairs, or their designees, are responsible for these reviews. An application for the use of a decedent's PHI for research is submitted to the HSPO (“Request for Review on Decedent’s Information”) or ORP (“Research on Decedent’s Information”), and approved by the IRB under expedited review.

The IRB may only approve such studies if all of the following requirements are satisfied:

- A representation from the researcher that the use or disclosure sought is solely for research on the PHI of decedents.
- Adequate documentation as specified by the IRB of the death of such individuals.
- A representation from the researcher that the PHI is necessary for the purposes of the proposed research.

Review of Request for Review of PHI Preparatory to Research

Because it may be necessary for a researcher to obtain access to and review PHI in order to prepare a research study, Title 45 CFR 164.512(i)(1)(ii) allows such review upon compliance with specified criteria. This provision might be used to design a research study, assess the feasibility of conducting a study, or to determine the eligibility of potential participants for a study. An application to request PHI preparatory to

research is submitted to the HSPO ("Request for Review Preparatory to Research") or ORP ("Data Collection for Reviews Preparatory to Research 45 CFR 164.512") and reviewed at the expedited level.

As the designated Privacy Boards for research at PSU, the IRBs have the authority to review and approve requests for the review of PHI preparatory to research. The IRB Chairs or their designees are responsible for these reviews.

The IRB may only approve such studies if all of the following requirements are satisfied:

- The use or disclosure of the PHI is solely to prepare a research study or for similar purposes preparatory to research;
- No PHI will be removed in any manner, including by means of copying or notes, from the patient records at PSU or other original source of PHI; and
- The PHI, for which access is sought, is necessary for the research purpose.

Use of a Limited Data Set/Data Use Agreement

A researcher may use and disclose PHI with some of the identifiers not usually allowed by 45 CFR 164.514(b)(2)(i), called a limited data set, if the researcher enters into a data use agreement with the recipient of the limited data set. At COM, the data use agreement is reviewed by the Office of Research Affairs and the HSPO. At UP, data use agreements related to HIPAA are reviewed by the Privacy Office and forwarded on to the Corporate Controller's Office for signatures. The ORP or HSPO receives a copy of the agreement for the IRB file. A central tracking system is used to catalog these agreements. A "Data Use Agreement" is available on the HSPO and ORP websites.

Review of Request for Waiver of Authorization

If a researcher proposes to obtain and use PHI in research without an authorization by the participant, the principal investigator must submit a request to the IRB for a waiver of the authorization requirement. Title 45 CFR 164.512(i)(1)(i) allows a waiver of authorization for the use of PHI upon compliance with specified criteria.

As the designated Privacy Boards for research at PSU, the IRBs have the authority to review and approve requests for a waiver of the authorization requirement. An application for a waiver of authorization is submitted to the HSPO ("Waiver of Authorization For Use of PHI Addendum") or ORP ("Waiver of Individual Authorization for Disclosure of Protected Health Information") and approved by the IRB under expedited or convened IRB review according to the criteria in 45 CFR 164.512(i)(2)(iv)(C). The convened IRB, the IRB Chairs or their designees, are responsible for these reviews.

An application for a waiver of authorization will be approved only if the IRB finds that the criteria in 45 CFR 164.512(i)(2)(ii) have been met. The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

- An adequate plan to protect the identifiers from improper use and disclosure;
- An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law;
- Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted under the HIPAA Privacy Rule;
- The research could not practicably be conducted without the waiver or alteration; and

- The research could not practicably be conducted without access to and use of the PHI.

Review of Request for Use of Business Associates Agreement
A researcher may engage business associates to assist in de-identifying PHI, to prepare limited data sets, or to perform data aggregation. The Privacy Rule [45 CFR 164.502 (and 45 CFR 164.504(e)] requires the researcher's covered entity to enter into a written contract with its business associates, allowing the researcher to disclose PHI to the business associate and allowing the business associate to use, create or receive PHI on the researcher's behalf. At COM, the business associates agreement is reviewed by a designated member of the Privacy Committee and the HSPO. At UP, all business associate agreements related to HIPAA are reviewed by the Privacy Office and forwarded on to the Corporate Controller's Office for signatures. The HSPO and the ORP receive a copy of the agreement for the IRB file.

L. Final Reports and Study Closure
When a study ends, is closed or canceled for any reason, a form must be submitted to the ORP or HSPO. At UP, to notify the IRB of research completion or closure, principal investigators submit a "Project Closeout Report for Research Involving Human Participants" or a Continuing Progress Report (CPR) form, which is considered the final report for the study and must contain all of the information described above in Section X.B. At COM, investigators must complete the CPR form regardless of whether or not the study is due for a continuing review. This form must also contain all of the information described above in Section X.B. These forms serve as notification to the ORP or HSPO that IRB approval of the study is no longer needed.

If the principal investigator does not complete a final report by the continuing review expiration date, an electronic memo is sent to the principal investigator (advisor, co-investigators and any other designee) the day following the expiration date stating that IRB approval has expired and the study automatically expired. This memo includes a reminder that no further human participant research activities may be conducted for the research unless IRB approval is first obtained. Copies of all memos are maintained in the IRB study file.

M. Urgent Review of Applications
Urgent review procedures may be invoked under limited circumstances (e.g., a principal investigator is faced with an immediate deadline beyond his or her control or a safety issue warrants immediate review). If the IRB staff permit urgent review of a study, the materials are distributed as soon as possible to IRB members to allow sufficient time for review prior to the meeting. The principal investigator and his/her advisor, if applicable, may be required to attend the meeting or be available via telephone or videoconference to answer any questions that arise. A quorum must be met for IRB actions to be taken. Meeting minutes will document the urgent review process.

N. Changes in Approved Research Initiated Without IRB Approval to Eliminate Apparent Immediate Hazards
Changes in approved research initiated without IRB approval to eliminate apparent immediate hazards to the participant require prompt reporting to the IRB (within 5 weekdays) and are reviewed according to the "IRB SOP Addendum: Reporting and Review of Unanticipated Problems Involving Risks to Participants or Others". These changes will be reviewed by the convened IRB at the next scheduled IRB meeting to determine whether the changes are consistent with ensuring the participants' continued welfare.

XI. IRB REVIEW AND APPROVAL CONSIDERATIONS

The IRB adheres to criteria for IRB approval for research specified in 45 CFR 46.111 and 21 CFR 56.111 when making study determinations. Before approval can be granted for initial and ongoing research, the IRB must determine that the following requirements are satisfied, if applicable.

A. Scientific Review

Scientific validity is taken into account during the review process when the study involves risk to the participants. In addition to scientific reviews at the departmental level, the IRB will judge scientific validity of each study, drawing on its own knowledge and disciplinary expertise. The IRB may also rely on the knowledge and disciplinary expertise of others with competence in special areas that require expertise beyond or in addition to that available on the IRB. This includes consultants independent of the investigators and the proposed research, reviews by funding agencies and other review committees.

B. Risks: Minimized and Reasonable Relative to Anticipated Benefits

The IRB considers the overall level of risk to participants while assessing the risk/benefit ratio during the evaluation process. An accurate description of the risks must be clearly outlined in the application with a corresponding explanation in the consent form for the participants. The possibility of unknown risks must be clearly stated, when applicable. Every possible precaution to minimize risks must be pursued by the investigator and outlined in the consent form as appropriate.

The IRB determines that risks are minimized by using procedures that are consistent with sound research design and do not expose participants to unnecessary risk. Scientific evidence is presented by the investigator in the application to support the expectation that anticipated benefits must be greater than anticipated risks. Special consideration is given by the IRB to protect vulnerable participants. Whenever appropriate, the research must utilize procedures that are already being performed on the participants for diagnostic or treatment purposes.

The level of risk is considered during requests for waiver or alteration of informed consent requirements or waiver of the requirement to obtain written documentation of consent. A waiver is not usually appropriate for FDA regulated test articles.

The research design and methodology are reviewed to determine that no obvious flaws would place participants at unnecessary risk. Experts are consulted when aspects of research design seem to pose a significant concern.

C. Equitable Selection of Participants

In making the determination for proper recruitment of the appropriate participant population, the IRB evaluates the purpose of the research, the research setting, the eligibility criteria, the expected outcome of the research and the following considerations:

- The IRB must determine that the selection of participants is equitable. This reflects the concept of 'Justice' from *The Belmont Report*. In making the determination for proper recruitment of the appropriate participant population as well as equitable selection of participants, the IRB will evaluate the purposes of the research, the effect of the recruitment procedures, the research setting, the inclusion/exclusion criteria, and the expected outcome of the research.

- The IRB is cognizant of the potential problems of research involving vulnerable populations. Generally, participants that stand no chance of benefiting from the research should not be selected to assume the risk unless the risk is minimal.
- The IRB will be mindful of the importance of including members of minority groups in research, particularly when the research holds out the prospect of benefit to the individual participant or the groups to which they belong. Non-English speaking participants cannot be systematically excluded because of inconvenience in translating informed consent forms. The IRB will also ensure that participants are not taken from one group of people because of convenience.
- The IRB will be mindful of the feasibility and desirability of including both women and men as research participants and will not arbitrarily exclude the participation of persons of reproductive age. Exclusions of such individuals must be fully justified and based on sound scientific rationale.

D. Review of Informed Consent Requirements

To approve research, the IRB determines that informed and voluntary consent is sought from each prospective participant or the participant's legally authorized representative, unless informed consent requirements can be waived or altered according to federal regulations. Informed consent is sought under circumstances that provide the participant or the participant's legally authorized representative with sufficient opportunity to consider whether or not to participate and minimize the possibility of undue influence.

Informed consent information is presented in a language that is understandable to the participant or the participant's legally authorized representative) and may not include any exculpatory language through which the participant is made to waive, or appear to waive, any of the participant's legal rights or through which the investigator, the sponsor, or PSU employees or agents are released from liability for negligence, or appear to be so released. Informed consent is obtained prior to initiation of any clinical screening procedures.

E. Documentation of Informed Consent

See Sections XII.A-H.

F. Waiver or Alteration of Informed Consent Requirements

See Section XII.E.

G. Waiver of Documentation of Informed Consent

See Section XII.E.

H. Obtaining Informed Consent from Non-English Speakers

See Section XII.D.

I. Obtaining Informed Consent from Participants Unable to Read

See Section XII.H.

J. Review of Plans for Data and Safety Monitoring

The IRB determines, when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants. The IRB requires a data safety monitoring plan (DSMP) be submitted for review and approval when research involves greater than minimal risk. The DSMP describes how the investigator plans to oversee the research participant's safety and welfare and

how adverse events will be characterized and reported. The purposes of the DSMP are to promote participant safety and to protect study integrity and validity. The level of detail in the DSMP should be based on the degree of risk incurred by the research participants. Low risk studies may have simple plans but all plans should contain at a minimum the following:

- A description and assessment of the study risks;
- A description of anticipated adverse events, including any grading mechanism to be used;
- A description of the reporting mechanisms for adverse events, including timing;
- Specification of who will be notified of adverse events, e.g., IRB, NIH, or FDA;
- Identification of person(s) responsible for identification, documentation and reporting of adverse events;
- Mechanism to inform all pertinent groups of any actions taken by the principal investigator in response to adverse events and any actions taken or recommended by the IRB during continuing review;
- Procedures which will be utilized to monitor participant safety, (e.g., evaluations and laboratory tests);
- Stopping rules which define critical thresholds for stopping or modifying the study;
- A description of data and the specific data to be monitored;
- Procedures for analysis and interpretation of the data;
- Mechanisms to protect data and ensure confidentiality;
- Defined frequency of review for summarized safety and aggregate analysis of data, and explanation of who will perform the review, e.g., principal investigator, medical monitor, clinical trial team, data safety monitoring board, or sponsor monitoring board; and
- Procedures for communicating recommendations from an external monitoring body to the IRB and investigative sites.

The DSMP will be reviewed by the IRB as a component of the protocol review to assure the adequacy of the DSMP in relationship to the size, complexity and level of risk of the proposed research. An independent data safety monitoring board (DSMB) may be required as a component of the DSMP for studies with large participant numbers, multiple sites, highly toxic therapies, dangerous procedures, high expected rates of morbidity and mortality in the study population, or high chance of early termination of the study. The IRB will review the qualifications and experience of the person responsible for data safety monitoring or the members of the DSMB. The IRB may make recommendations regarding expertise, frequency of meetings, etc., to the principal investigator for the enhancement of human participant protections. The IRB may request additional information or clarification regarding the DSMP or DSMB. The IRB has the authority to require a data safety monitoring board (DSMB) as a condition for approval of research where it determines that such monitoring is needed. When DSMBs are utilized, the IRB relies on current statements or reports from the DSMB indicating that it has reviewed study-wide interim findings and any recent literature that may be relevant to the research.

K. Privacy and Confidentiality

The IRB adheres to 45 CFR 46.111, 21 CFR 56.111, 45 CFR 160 and 45 CFR 164 when determining the adequacy of measures to protect privacy and confidentiality.

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

Privacy is defined in terms of having control over the extent, timing and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. The possibility that research may invade the privacy of individuals should be considered when evaluating a research study. Under certain circumstances, an invasion of privacy may even present a risk of serious harm to participants (e.g., as when the research obtains information about participants that would, if disclosed by the researcher, jeopardize jobs or lead to prosecution for criminal behavior). Under other circumstances, an invasion of privacy can be a moral wrong, or, at least in theory, provide cause for legal action against a researcher or institution. It is the responsibility of the researcher to be sensitive to the issues involved with privacy and to consider them appropriately in designing the study.

In their IRB applications, investigators provide information pertaining to provisions that will be taken to ensure privacy and confidentiality, including (1) what measures will be taken to minimize loss of privacy, (2) where study procedures will occur, (3) how data will be protected, (4) who will have access to data, (5) to whom identifiers will be disclosed, (6) whether an identifier code list will be used, (7) who will have access to said list, (8) what provisions will be made for the data at study completion, and (9) whether the nature of the data could lead to adverse consequences for participants should confidentiality be breached. In reviewing privacy and confidentiality protections, the IRB considers the nature, probability, and magnitude of harms that would likely result from a disclosure of information outside the research. The IRB evaluates the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. Specific questions the IRB considers are identified in the "Summary Guide to IRB Review Criteria".

L. Additional Safeguards for Vulnerable Participants

See Section XVI.

M. Information the Investigator Provides to the IRB

The IRB expects the investigator to thoroughly complete the initial application, Modification Request Form, and Continuing Progress Request (CPR) form.

N. Criteria for Requiring Review More Often than Annually

In specifying an approval period of less than one year, the IRB defines the period with either a time interval or a maximum number of participants (i.e., after three months or after 10 participants). The meeting minutes clearly reflect these determinations regarding risk and approval period. The IRB may require review more often than annually for:

- Research that involves withdrawal of therapy when there is significant risk of morbidity or mortality
- Research that involves an invasive surgical procedure
- Research that presents a serious risk of impairment
- Research in which there are serious risks to participants and no potential benefits
- More than minimal risk research involving prisoners, or
- More than minimal risk research involving cognitively impaired adults

O. Independent Verification from Sources Other than the Investigator that No Material Changes have occurred since the Previous Review

Protecting the rights and welfare of participants sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes occur during the IRB-designated

approval period. Additional sources may include investigational pharmacy records, incident reports, radiation safety or source documents, as well as information from staff, research participants, families, sponsors or others. The IRB may also require the investigator to seek additional expertise or supervision to assess participant safety.

The IRB may require verification of information provided during a continuing review when:

- The information provided by the investigator is inconsistent either internally or with other information known to the IRB,
- The information provided by the investigator is suspected of being incorrect, or
- The investigator has had a determination of serious or continuing non-compliance in the past year.

In making the determination about independent verification, the IRB may require that the verification takes place at predetermined intervals during the approval period or may retrospectively require such verification at the time of continuing review.

P. Advertising and Recruitment Materials and Procedures

The IRB reviews the information contained in recruitment materials and the mode of its communication to determine that the procedure for recruiting participants is not coercive. Recruitment is directly related to the informed consent process, must be designed to assure that informed consent is given freely, and is without coercion or undue influence. Specifically, the IRB reviews recruitment verbiage, and the final advertising media to ensure recruitment materials do not:

- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol/application;
- Make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, or device, if applicable;
- Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation, if applicable;
- Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational, if applicable;
- Promise “free medical treatment” when the intent is only to say participants will not be charged for taking part in the investigation, if applicable;
- Emphasize the payment amount by such means as larger font or bold type; and
- Include exculpatory language.

For additional information, see IRB Guideline III “Participant Recruitment and Advertising” on the ORP website or “Recruitment of Research Participants” on the HSPO website.

Q. Payment to Research Participants

The IRB considers the compensation offered to research participants when evaluating the appropriateness of the informed consent process to ensure that informed consent is sought under circumstances that minimize the possibility of coercion or undue influence.

Payment to research participants for participation in studies is not considered a benefit. Rather, it is considered compensation for time and inconvenience or a recruitment incentive. The amount of compensation should not be based on the risk of study participation. Investigators follow the payment

procedures and record keeping requirements as outlined in PSU Procedure CR2078 “Payments to Research Participants” when providing compensation to research participants.

The amount and type of compensation should be based on:

- The complexity of the research as it relates to participant inconvenience;
- The type and number of procedures to be performed;
- The time involved;
- The anticipated discomfort of the study; and
- The participant population.

When reviewing a research study where participants will receive payments for their participation, the IRB considers the following:

- The amount and schedule of all payments should be presented for review at the time of initial review. The IRB reviews both the amount of compensation and the schedule of payment to assure that neither are coercive nor present undue influence for initial or continued participation in the study.
- Any credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. The participants should be compensated in proportion to their time and inconvenience as a result of participation in the research study.
- Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to participants who had withdrawn before that date.
- While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such incentive is not coercive.
- The IRB will determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.
- All information concerning payment including the amount and schedule of payment(s) should be described in the informed consent document.
- While advertisements may state that participants will be compensated, reimbursed for expenses, and/or state the amount of compensation, it should not emphasize the payment or the amount to be paid.
- Any alterations in research participant compensation must be reported to the IRB for review and approval prior to implementation as an amendment.
- Compensation for participation in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved and marketed.

Penn State employees may take part in human participant research. However, participation may not take place during work hours. Employees must either take vacation if participation occurs during normal work hours or take part on their own time. In addition, payment for participation cannot be tied to an employees’ salary or hourly wage.

R. Acceptable and Unacceptable Payment Arrangements

The IRB does not review payment arrangements among investigators, sponsors, organizations, and those referring research participants. At COM, these payments are reviewed by and arranged through the Office of Research Affairs. At UP, the Office of Sponsored Programs reviews and provides the arrangements for these payments. There is no direct payment to investigators. Instead, payments designated for investigators are transferred to the budget of the department in which the investigator is employed and the department determines the use of the monies. No salaries within the institution are changed due to payments among the aforementioned groups. Payment in exchange for referral of potential participants and/or payment tied to the rate or timing of enrollment ("bonus payments") is prohibited.

S. Extra Costs to Participants or to Third Party Payers

Where applicable, extra costs for participation in the research whether for participants or third parties must be disclosed in the consent form.

T. Certificates of Confidentiality (CoC)

Where research involves the collection of highly sensitive information about individually identifiable participants, the IRB determines if special protections are needed to protect participants from the risks of investigative or judicial processes. In such situations, the IRB may require that the investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). If the study involves an Investigational New Drug Application or an Investigational Drug Exemption, the sponsor or investigator can request a CoC from the FDA. The CoC protects against the involuntary release of sensitive information about individual participants for use in federal, state, or local civil, criminal, administrative, legislative or other legal proceedings.

A CoC does not prohibit voluntary disclosure of information by a participant. Investigators are still required to report communicable diseases to local authorities and obligated to break confidentiality if a participant is a threat of harm to him/herself or others. In addition, the CoC does not protect against the release of information for audit purposes. Conditions for the release of information must be stated clearly and explicitly in the informed consent form.

U. Qualifications of Investigators

The IRB determines that the investigators have adequate knowledge, processes, personnel and facilities to conduct human participant research according to federal, state, and local laws and regulations, ethical principles of The Belmont Report, and institutional policies. The IRB also determines that the investigators are qualified by education, training and expertise to assume responsibility for the proper conduct of the research study.

XII. INFORMED CONSENT AND DOCUMENTATION

Informed consent is required for all human participant research unless the activity meets regulatory findings stipulated for waiver/alteration of informed consent or waiver of documentation of consent. Informed consent presumes two simultaneous concepts: informed decision-making and voluntary participation.

To assist individuals conducting research, ORP and HSPO provide information on their websites regarding the informed consent process. Templates and instructions are available including guidelines for

the consent process and developing an informed consent document, suggested wording, and additional instructions for specific circumstances.

The required and additional elements of consent are incorporated in reviewer checklists to assist the IRB in evaluating the consent disclosures and ensuring that the required disclosures are made. At COM, reviewers are instructed to follow the "Summary Guide to IRB Review Criteria" for a list of informed consent requirements and then document their review using the applicable reviewer checklist.

During the review of the informed consent process, the IRB requires the following per 45 CFR46.116 and if applicable 21 CFR 50.20.

- Adequate opportunity is provided to the participant or the participant's legally authorized representative to read the consent document before it is signed.
- The consent process minimizes the possibility of coercion or undue influence.
- The consent discussion is in a language understandable to the participant or the participant's legally authorized representative.
- The information being communicated to the participant or the participant's legally authorized representative during the consent process does not include any exculpatory language through which the participant or the participant's legally authorized representative is made to waive or appear to waive any of their legal rights.
- The information being communicated to the participant or the participant's legally authorized representative during the consent process does not include any exculpatory language through which the participant or the participant's legally authorized representative releases or appears to release the investigator, the sponsor, the institution, or it's agents from liability for negligence.
- The consent discussion and document, if applicable, embodies the required elements of informed consent except those studies for which a regulatory basis is stated for the waiver or alteration.

A. Required Elements

Informed consent disclosures must include all of the following elements, when applicable, as required by 45 CFR 46.116(a) or 21 CFR 50.25(a) as applicable.

- Statement that the study involves research
- Explanation of the purpose
- Expected duration of participation
- Description of procedures to be followed
- Identification of any experimental procedures
- Description of any reasonably foreseeable risks or discomforts to the participant
- Description of benefits to the participant or others that may be reasonably expected from the research
- Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant
- Statement describing the extent to which confidentiality of records identifying the participant will be maintained.
- For FDA regulated research, a statement that notes the possibility that the Food and Drug Administration may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and whether any medical treatments are available if injury occurs during study participation

- Explanation of whom to contact for answers to questions related to research and rights of research participants
- Explanation of whom to contact in the event of a research-related injury to participant
- Statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

B. Additional Elements

As noted below, one or more of the following elements shall also be provided, per 45 CFR 46.116(b) or 21 CFR 50.25(b) as applicable:

- If the risk profile of any research–related interventions is not well known or the research involves investigational drugs or devices: A statement that the particular treatment or procedures may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable;
- If the research includes women of child bearing potential or pregnant women, and the risk profile of any research interventions or interactions on embryos and fetuses is not well known: A statement that the particular treatment or procedure may involve risks to the embryo or fetus, if the participant is or may become pregnant, which are currently unforeseeable;
- If there are anticipated circumstances under which the participant's participation will be terminated by the investigator without regard to the participant's consent: Anticipated circumstances under which participation may be terminated by the investigator without the participant's consent;
- If there are costs to the participant that may result from participation in the research: A statement describing any additional costs associated with study participation;
- If there are adverse consequences (physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research: A statement describing the consequences of a participant's decision to withdraw from the research;
- If there are adverse consequences (physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research: A statement describing the procedures for an orderly termination of participation;
- Unless significant new findings during the course of the research which may relate to the participant's willingness to continue participation are unlikely: A statement that new findings developed during the course of the research that may relate to the participant's willingness to continue in the research study will be provided to the participant;
- Unless the approximate number of participants involved in the study is not important to a decision to take part in the research: A statement providing the approximate number of participants involved in the study.
- The amount and schedule of payments.

The IRB may also require that additional elements or information be given to the prospective participants when, in the IRB's judgment, the information would meaningfully add to the protection of the rights and welfare of the research participant.

At COM, when the research includes the use and disclosure of participants' protected health information the informed consent form may include the elements required by 45 CFR 164.508 (c). The HSPO has wording available on their website for consent forms that need to include HIPAA language.

At UP, investigators may use a separate authorization form or include the HIPAA language in the consent form. The ORP has a separate HIPAA authorization template and consent form wording available on their website.

C. Documentation of Informed Consent

It is the policy of the PSU IRB that informed consent is documented in writing unless specifically waived by the IRB as determined in the IRB review and approval process. The IRB determines that documentation of consent will be in accordance with DHHS 45.CFR 46.117 and FDA 21 CFR 50.27, if applicable. In most circumstances, the IRB requires that informed consent is documented by the use of a written consent form approved by the IRB and signed by the participant or participant's legally authorized representative. This consent form must include the required elements of informed consent, in addition to any applicable additional elements that are required by the federal regulations. This form may be read to the participant or the participant's legally authorized representative. However, the investigator should allow the participant or the legally authorized representative adequate opportunity to read and consider the consent document before it is signed.

In cases of signed informed consent, PSU policy requires the signature of a participant or the participant's legally authorized representative who may provide legally effective informed consent. In addition, the IRB requires the signature of an investigator or research staff member who is obtaining consent. For FDA regulated research, the consent document must be signed and dated by the participant or the participant's legally authorized representative. A copy of the consent document will be given to the participant or the participant's legally authorized representative. For research subject to the FDA regulations, a copy of the signed consent document will be given to the participant or the participant's legally authorized representative.

The signature of a witness is required when a participant or participant's representative is unable to read or when the IRB authorizes the use of a short form written consent procedure for limited English speaking individuals. The witness observes the informed consent process and signs a statement attesting to the consenting process being done voluntarily on the part of the research participant, as well as being accurate.

A consent form addendum is used to inform enrolled participants of significant new findings that may have a bearing on their willingness to continue participation in the study. The addendum to consent form focuses on the new information participants need to consider when making a decision about their continued participation in the study.

D. Limited English Speaking Participants

Informed consent information must be presented in a language understandable to the prospective participant or the participant's legally authorized representative. Routine ad-hoc translations of the consent document may not be substituted for a written translation.

Written Translation

When recruitment for the research is anticipated for a particular non-English speaking population, a translation of the written informed consent document should be provided to the prospective participants or their legally authorized representative in a language they understand. The written translations should be made by a reliable source. Documentation from an individual not associated with the research verifying

the translation may be requested by the IRB. Investigators are asked to provide the credentials of the individuals translating the form and verifying its accuracy if applicable. The IRB must approve the translated consent form before use.

Oral Translation

If a non-English speaking individual is unexpectedly encountered and a translated IRB-approved consent form is not available, the investigators may use an oral translation process to provide the information in a language understandable to the prospective participant or the participant's legally authorized representative. The oral translation should include presentation of the elements of informed consent disclosure required by regulations (i.e., the basic and additional elements, outlined above). The oral translation must be made in the presence of an impartial witness who is fluent in both English and the language of the prospective participant or the participant's legally authorized representative. If a translator is used for the oral translation, this individual may serve as the witness if he or she is impartial to the research.

When an oral presentation of informed consent information is used, the participant or the participant's legally authorized representative must be provided with both:

(1) a short form written informed consent document which states that the required elements of consent have been presented orally to the participant or the participant's legally authorized representative; and

(2) a written summary of the information that is presented orally. The IRB-approved English language informed consent document may serve as the written summary.

The IRB must review and approve all foreign language versions of the short form informed consent documents prior to use. For studies reviewed by the convened IRB, expedited review of these versions is acceptable if the convened IRB has already approved the research study and the written summary, i.e., the English language informed consent document.

Documentation requirements

Short form consent document: The IRB-approved short form consent document is written in a language understandable to the prospective participant or the participant's legally authorized representative and includes the following:

- the invitation to participate in research;
- the categories of information that will be explained orally;
- contact information in event of concerns about a research injury or questions about the research or the participant rights;
- the voluntary nature of participation and clarification that there will be no penalty or loss of benefits for refusal to participate; and,
- an explanation that signing the form denotes agreement to participate.

The short form must be signed by the participant or the participant's legally authorized representative providing consent and the witness. For FDA-regulated research, the short form must be signed and dated by the participant or the participant's legally authorized representative and the witness.

Written summary: The written summary should embody the basic and required additional elements of informed consent disclosure (i.e., the English language informed consent document). The written summary must be signed by the person obtaining consent as authorized under the protocol and the

witness. For FDA-regulated research, the written summary must be signed and dated by the person obtaining consent and the witness.

The participant or the participant's legally authorized representative receives copies of both of these signed documents.

E. Alterations to Informed Consent or Documentation

Waiver or Alteration of Informed Consent

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent outlined above, or waives the requirement to obtain informed consent as outlined in 45 CFR 46.116(c) provided the IRB finds and documents:

- The research is not subject to FDA regulation.
- The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate or otherwise examine:
  - Public benefit or service programs;
  - Procedures for obtaining benefits or services under those programs;
  - Possible changes in or alternatives to those programs or procedures; or
  - Possible changes in methods or levels of payment for benefits or services under those programs; and
- The research could not be practicably carried out without the waiver or alteration.

The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent outlined above, or waives the requirement to obtain informed consent as outlined in 45 CFR 46.116(d) provided the IRB finds and documents:

- The research involves no more than minimal risk to the participants; **and**
- The waiver or alteration will not adversely affect the rights and welfare of the participants; **and**
- The research could not practicably be carried out without the waiver or alteration; **and**
- Whenever appropriate, the participants will be provided with additional pertinent information after participation; **and**
- The research is not subject to FDA regulation

The IRB may waive the requirement to obtain informed consent for research that involves human specimens that are not individually identifiable for FDA-regulated in vitro diagnostic device investigations as per FDA guidance (OMB Control No. 0910-0582) provided the IRB finds and documents:

- The study involves an in vitro diagnostic device investigation.
- The testing is noninvasive.
- The testing does not require an invasive sampling procedure that presents significant risk.
- The testing does not by design or intention introduce energy into a participant.
- The device is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- One of the following is true:
  - For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."

    - For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."
- The study uses one of more of the following leftover specimens:
    - Specimens collected for routine clinical care or analysis that would have been discarded.
    - Specimens obtained from specimen repositories.
    - Leftover specimens that were previously collected for other research purposes.
- The specimens are not individually identifiable as both of the following are true:
    - The identity of the participant is not known to the investigator or any other individuals associated with the investigation, including the sponsor.
    - Neither the investigator nor any other individuals associated with the investigation, including the sponsor can readily ascertain the identity of the participant.
- One of the following is true:
    - The identity of the participant is not known to and may not readily be ascertained by the investigator or any other individuals associated with the investigation, including the sponsor.
    - If the specimen is coded, neither the investigator(s) nor any other individuals associated with the investigation or the sponsor can link the specimen to the participant from whom the specimen was collected, either directly or indirectly through coding systems.
- Either of the following are true:
    - The specimens are not accompanied by clinical information.
    - Clinical information that accompanies the specimens does not make the specimen source identifiable to the investigator or any other individual associated with the investigation, including the sponsor
- The individuals caring for the patients are different from those conducting the investigation and do not share information about the patient with those conducting the investigation.
- The individuals caring for the patients do not share information about the patient with those conducting the investigation.
- The specimens are provided to the investigator(s) without identifiers.
- The supplier of the specimens has established policies and procedures to prevent the release of personal information.
- The study has been reviewed by an IRB in accordance with 21 CFR Part 56, except for determining compliance with 21 CFR Part 50.
- The research is NOT subject to DHHS regulation.

Waiver of the Requirement for Documentation of Informed Consent

The IRB may waive the requirement to obtain a signed consent form, in accord with 45 CFR 46.117(c) when:

- The only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality, each participant will be asked whether the participant wants documentation linking the participant with the research, the participant's wishes will govern, and the research is not subject to FDA regulation; **or**

- The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

For research subject to FDA regulations (21 CFR 56.109(c)(1), the IRB may, for some or all participants, waive the requirement for documentation of informed consent if it finds that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context.

In cases where the documentation requirement is waived, the IRB reviews a written summary of the information provided to participants and considers whether to require the investigator to provide participants with a written statement regarding the research. That document, if required by the IRB, is reviewed and approved by the IRB.

When the IRB approves a consent procedure that does not require, or which alters, some or all of the elements of informed consent outlined above, or waives the requirement for a signed consent form the IRB determines and documents that the specific findings are met as required by the regulations. If the request is reviewed at a convened IRB meeting, the meeting minutes document the IRB's findings regarding the decision to grant a waiver. Similarly, if the study meets the criteria for review under expedited procedures, the reviewer documents the findings and decision to grant the waiver.

F. Passive Consent

Passive consent, where the lack of an objection to research participation would be considered an agreement to participate, is not recognized in the federal regulations. Active consent must be obtained unless the convened IRB determines that the study meets the criteria to waive the requirement for the consent process and grants a waiver.

G. Assent

See Section XVI.A.

H. Witness to Consent

A witness to the informed consent process is required when an informed consent discussion will be conducted with a prospective participant, or participant's representative, who is eligible and capable of providing legally effective informed consent, but the individual is:

- Unable to read the consent form; *OR*
- Non-English speaking and a Short Form Consent and oral translation process is used.

To qualify as a witness for the consent process, an individual must be an impartial third party who is not connected with the research such as, a non-research team employee, a relative of a participant, or person similarly unconnected with the research. The witness must be present during the entire informed consent discussion, while the consent form and any other written material and information for the participant is read, explained and discussed. The role of the witness is to observe that the information in the consent form and other material about the research is explained accurately, that the potential participant or participant's legally authorized representative understands, and that the decision to participate is made freely.

After witnessing the informed consent process, the witness signs a witness statement attesting to the consenting process being done voluntarily on the part of the research participant, as well as being

accurate. The witness statement may be incorporated in the IRB-approved informed consent document, or a separate witness form may be signed and attached to the informed consent form, becoming a part of the consent documentation for the participant.

XIII. AUTHORIZATION FOR THE USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI)

When human participant research includes the use and disclosure of protected health information (PHI), an authorization for use of the information is required from the participants. The authorization may be: (1) part of the research informed consent form or (2) a stand-alone document. Suggested Consent Wording containing the elements required by the Health Insurance Portability and Accountability Act (HIPAA; Privacy Rule) may be located on the HSPO website. The ORP website offers both suggested consent wording and a standalone Authorization form ("Authorization to Use and Disclose Protected Health Information for Research Purposes").

To assist those conducting research, the ORP and HSPO have information available on their websites regarding compliance with HIPAA and the authorization process.

A. Required Elements

The informed consent form or the authorization document should include the following elements [45 CFR 164.508(c)]:

- A description of the information to be used or disclosed that identifies the information in a specific and meaningful fashion.
- The name or other specific identification of the person(s) or class of persons authorized to make the requested use or disclosure.
- The name or other specific identification of the person(s) or class of persons to whom PSU may make the requested use or disclosure.
- A description of each purpose of the requested use or disclosure.
- An expiration date or an expiration event that relates to the individual or the purpose of the use or disclosure. The statement "end of the research" or "none" is sufficient if authorization includes use or disclosure of PHI for creation of a research repository or database.
- Signature of the participant and date. If the authorization is signed by a personal representative of the participant, a description of the representative's authority to act for the participant.
- The following statements must be included in the authorization:
  - The participant's right to revoke the authorization in writing, and the exceptions to the right to revoke
  - A description of how the individual may revoke the authorization
  - The consequences to the participant if he/she refuses to sign the authorization
  - When PSU can condition enrollment on failure to obtain authorization
  - The potential for information disclosed pursuant to the authorization to be subject to re-disclosure by the recipient and no longer be protected by the federal regulations

The information in the authorization form must be written in plain language and understandable to the participant.

B. Alternatives to Authorization for the Use of PHI

The IRB adheres to criteria for approval of the use and disclosure of protected health information for research purposes for which an authorization or opportunity to agree or object is not required [45 CFR 164.512(i)].

Waiver of Authorization for the Use of PHI [45 CFR 164.512(i)(1)(i)]

If a research study proposes to obtain and use PHI in research without an authorization, the principal investigator must submit a request for a waiver of the authorization requirement to the IRB for review and approval. At UP, investigators may submit the "Waiver of Individual Authorization for Disclosure of Protected Health Information" form located on the ORP website. For additional information, see PSU Policies RA22, "HIPAA and Research at Penn State University," and RA23, "HIPAA and Research at The Milton S. Hershey Medical Center and Penn State College of Medicine".

Review Preparatory to Research [45 CFR 164.512(i)(1)(ii)]

Because it may be necessary for a researcher to obtain access to and review PHI in order to prepare a research study, HIPAA rules allow such a review upon compliance with specified criteria. An application for review of PHI preparatory to research must be submitted to the IRB for review and approval. At UP, investigators may submit the "Data Collection for Reviews Preparatory to Research 45 CFR 164.512" form located on the ORP website. For additional information see PSU Policies RA22, "HIPAA and Research at Penn State University," and RA23, "HIPAA and Research at The Milton S. Hershey Medical Center and Penn State College of Medicine".

PHI of Decedents [45 CFR 164.512(i)(1)(iii)]

An application for the use of PHI from decedents must be submitted to the ORP or HSPO prior to engaging in the research. In order to gain access to the PHI, the principal investigator needs to demonstrate that the use or disclosure being sought is solely for research on the PHI of decedents, adequate documentation of the death of such individuals, and that the PHI for which use or disclosure is sought is necessary for the purposes of the proposed research. At UP, investigators may submit the "Research on Decedent's Information" form located on the ORP website.

XIV. SOCIAL SCIENCE RESEARCH

A. Social and Psychological Harm

When reviewing behavioral and social sciences research, the IRB ensures that investigators have made every attempt to minimize risks and possible harms to participants, whether social, psychological or physical. Potential risks to participating in behavioral and social science research could be but are not limited to breach of confidentiality, invasion of privacy, embarrassment, and risk to reputation, employability, and insurability.

B. Confidentiality Concerns

The IRB follows 45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7) when determining the adequacy of the plan provided by researchers to protect the privacy of participants and maintain confidentiality of the data. If a research study will involve protected health information, all privacy and confidentiality mandates outlined in the HIPAA regulations (45 CFR 160/164) are also followed.

In accordance with 45 CFR 46.116 and 21 CFR 50.25, the IRB takes into account the description of the extent, if any, to which confidentiality of records identifying the participant will be maintained when reviewing the informed consent form. For research that falls under FDA jurisdiction, a statement that the FDA may inspect the research records is added to the consent form.

Investigators are instructed to store and secure their data in a confidential manner as outlined in their application. If possible, the research is conducted without any type of identifiers associated with the data. If data are gathered with personal identifiers, whenever possible, personal identifiers are removed from data and code numbers are used with master code lists. The master code list and signed informed consent forms are stored separately from the data. In accordance with federal regulations, researchers must maintain their signed informed consent forms for a minimum of three years from the close of the study or if the study falls under HIPAA regulations, for a minimum of six years. Study sponsors may have additional requirements regarding retention of data and consent forms.

For research involving the use of audio, video or digital recordings, researchers submitting to the ORP must adhere to IRB Guideline XI "Research Involving Audio, Video or Digital Recordings of Research Participants", which is available on the ORP website. Researchers must inform participants in the informed consent form where recordings will be stored, who will have access to them, and the year by which the tapes will be destroyed. Researchers have the option to archive recordings or use recordings in future research, classroom or conference presentations, etc. In order to archive recordings, researchers must provide a justification to the IRB for archiving the recordings and give the participant, in the informed consent form, the option of declining or allowing the recordings to be archived or used for future research, educational or conference presentations.

The IRB may request a researcher to obtain a Certificate of Confidentiality from the NIH if the research is of a sensitive nature and protection is warranted.

XV. IRB REVIEW OF RESEARCH USING DATA OR SPECIMENS

A. Research Using Data

Chart Reviews

A human participant is defined, in part, as a living individual about whom an investigator conducting research obtains identifiable private information. Therefore, medical or other chart/record review research requires ORP/HSPO oversight to determine if the study is human participant research.

Retrospective Chart Reviews

Retrospective chart review studies involve reviewing data, documents or records collected in the past and existing at the time the research is proposed and initiated. Such research may be exempt if the information is publicly available or if the information is recorded by the researcher in such a manner that participants cannot be identified, either directly or through identifiers linked to the participants. If the research does not qualify as exempt, the IRB may review the research using expedited procedures, if the protocol meets all applicability criteria and involves procedures in one or more categories of research for expedited review. If the research entails greater than minimal risks to privacy and confidentiality, then convened IRB review is required.

For retrospective chart review studies the IRB may: (1) approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent or waives the requirements to obtain informed consent by documenting that the research is not subject to FDA regulation and meets the criteria set forth in 45 CFR 46.116(d) or (2) require prior written informed consent of involved participants.

Prospective Chart Review

Prospective chart review studies are designed to collect information about outcomes or events that occur in the future, e.g., after the date of the IRB application. Prospective studies using information that will exist in the future do not qualify for exemption because the data in these studies are not in existence at the time the research is proposed and initiated. These studies may qualify for expedited review if the information will be collected solely for non-research purposes (such as medical treatment or diagnosis) and the information being collected for the research is not considered sensitive and any potential breach of confidentiality would not be damaging to the participant, and if the protocol meets all applicability criteria and involves procedures in one or more categories of research for expedited review. If the research entails greater than minimal risks to privacy and confidentiality, then convened IRB review is required.

In general, research involving prospective data collection requires prior written informed consent of involved participants. In some research studies, the IRB may approve a consent procedure, which does not include, or which alters, some or all of the elements of informed consent or waives the requirement to obtain informed consent by documenting that the research is not subject to FDA regulation and meets the criteria set forth in 45 CFR 46.116(d) for waiver or alteration of the requirement for informed consent.

Secondary Data Analysis

Any research that involves the use of secondary data where individual participant records are involved requires ORP/HSPO oversight to determine if the research qualifies as one of the following: (1) human participant research exempt from IRB review, (2) not human participant research or (3) the research requires IRB review.

For example, an investigator who plans to analyze an existing data set obtained from another source submits an application for IRB review if the data set contains records about individual human participants. If the data set contains no identifying information (this includes direct or linked code numbers), the investigator may submit an application to the IRB for a determination that the activity is not human participant research. If the data set is publicly available, the study may be exempt from IRB review. If the research does not qualify as exempt, the IRB may review the research using expedited procedures, if the study meets all applicability criteria and involves procedures in one or more expedited categories. If the research involves greater than minimal risks to privacy and confidentiality, convened IRB review is required.

For secondary data analysis research the IRB determines if the information can be used without obtaining informed consent from the participants. The IRB examines the conditions of informed consent under which the data were originally obtained. The IRB may approve an alteration or waiver of the requirement to obtain informed consent provided the IRB finds and documents that the research is not subject to FDA regulation and meets the criteria set forth in 45 CFR 46.116(d) for waiving the requirement for informed consent.

Case reports
Case reports generally provide anecdotal observations of a disease on individual patients and do not contribute to generalizable knowledge. Provided that appropriate steps are taken to assure confidentiality of patient information, the review of case reports for human participant protection issues is not required.

B. Research Using Specimens
Human participant research studies involving either existing specimens or prospectively collected specimens require ORP/HSPO oversight to determine if the study qualifies as one of the following: (1) human participant research exempt from IRB review, (2) not human participant research, or (3) the research requires IRB review. Specimen research includes studies of blood samples, other body fluids, fresh or preserved tissue including frozen tissue or paraffin blocks.

At COM, the release of tissue or use of pathologic specimens from Anatomic Pathology for research purposes requires prior authorization by Anatomic Pathology and cannot occur until the clinical pathology requirements are adequately addressed. Principal investigators must complete a "Use of Human Tissue for Research Form" and submit it to the Department of Pathology for approval.

At UP, studies involving the use of human blood, body fluids and tissues require review and approval by the Biomedical Institutional Review Board (IRB), unless the activity involves no interaction or intervention with participants and involves no private identifiable information.

All studies involving the use of human blood, body fluids and tissues require review and approval by the Institutional Biosafety Committee (IBC). PSU Policy SY24, "Use of Biohazardous Materials in Research and Instruction," provides guidance to ensure safe handling, storage, and disposal of potentially biohazardous materials used in University research or instructional studies. At UP, principal investigators must complete an "Application for the Use of Biohazardous Materials in Research" and undergo a laboratory inspection as well as training on blood-borne pathogens. Training is provided by the Environmental Health & Safety Office (EHS). At COM, principal investigators must complete a "Biological Safety and Recombinant DNA (BSRD) Assurance Form" and undergo a laboratory inspection as well as training. Training is provided by the Safety Office.

Research involving existing tissue specimens using archived or banked tissue samples collected in the past and existing at the time the research is proposed and initiated
This research requires ORP/HSPO oversight to determine if the study qualifies as one of the following: (1) human participant research exempt from IRB review, (2) not human participant research, or (3) the research requires IRB review.

Such research may be exempt if the specimens are publicly available or if the specimens are labeled in such a manner that participants cannot be identified, either directly or through identifiers linked to the participants. If the research study does not qualify as exempt, the IRB may review the research using expedited procedures, provided the research meets all applicability criteria and involves procedures in one or more expedited categories. If the research involves greater than minimal risks to privacy and confidentiality, convened IRB review is required.

For research using existing specimens, the IRB may: (1) approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent provided the IRB finds and documents that the research meets the criteria set forth in 45 CFR 46.116(d) for waiving the requirement

for informed consent and is not subject to FDA regulation or (2) require prior written informed consent of involved participants.

For research using tissue specimens that have been previously collected for a different research study, the IRB determines if the specimens can be used without obtaining informed consent from the participants. The IRB first examines the conditions of informed consent under which the specimens were originally obtained. It may be that the proposed research is permissible under the original terms of consent. If this is not the case, the IRB may approve a waiver of the requirement to obtain informed consent provided the IRB finds and documents that the research meets the criteria set forth in 45 CFR 46.116(d) for waiving the requirement for informed consent and is not subject to FDA regulation. Exceptions to this may be allowed if the research involves human specimens that are not individually identifiable for FDA-regulated in vitro diagnostic device investigations as per FDA guidance (OMB Control No. 0910-0582). If the IRB does not approve a waiver or alteration of consent, the IRB may require written informed consent of involved participants.

Research involving prospectively collected specimens e.g., after the date of the IRB application
Research using tissue samples or biological specimens obtained specifically for research purposes, which would not be collected otherwise, requires prior IRB review and approval of the study and requires written informed consent from the participant. This includes research in which either a procedure/collection is performed specifically to obtain the sample or the collection of extra material occurs at the time of a clinically indicated procedure.

The study may be eligible for expedited review, provided the research meets all applicability criteria and involves procedures in one or more expedited categories. If the research involves greater than minimal risk, convened IRB review is required. Informed consent should be obtained even if the tissue samples are to be used anonymously. With anonymous use of samples, participants should be told that their samples will not contain any identifying information and that they will not receive any results from their research tests.

Anonymous Samples
Studies involving the use of anonymous, discarded specimens as defined below may be exempt from the requirement for IRB oversight if it is determined by the IRB Chair or a designee that the research does not involve human participants as defined in the federal regulations. Human participants would not be involved when the specimens satisfy both of the following conditions:

- The material, in its entirety, was collected for purposes other than research (e.g., the material was collected solely for clinical purposes); and
- The material is provided to the investigators without any identifiable private data or information (i.e., no code or links of any sort may be maintained that would permit access to identifiable private data or information about the living individual from whom the material was obtained).

If the samples are used for FDA-regulated research, the study will require expedited review. Any concerns about risks to classes of participants could result in convened IRB review.

Identifiable Samples
Studies involving the prospective use of identified discarded specimens require prior IRB review and approval either by an expedited review process or by the convened IRB. If identifiers or links to identifiers are maintained, prior written informed consent will be required. However, the IRB may

approve a waiver of the requirement to obtain informed consent, provided the IRB finds and documents that the research is not subject to FDA regulation and meets the criteria set forth in 45 CFR 46.116(d) for waiving the requirement for informed consent.

C. Research Using Tissue and Data Banks or Repositories

Research studies aimed at setting up repositories of data and/or biological samples must be submitted for IRB review and approval prior to collecting information or specimens. The study may qualify as exempt. If the specimens are not identifiable, the study may be designated as not human participant research unless the samples are used for FDA-regulated research, in which case the study will require expedited review. A repository that will be used for human participant research should have written procedures for procuring data and/or samples (including recruitment, informed consent and authorization processes), storing data and/or samples, determining who will have access, and protecting personally identifiable information.

Written informed consent must be obtained from each donor-participant. The basic elements of informed consent that should be provided to the participant include:

- The operation of the repository
- The specific types of research to be conducted
- The conditions under which data and/or specimens will be released to recipient-investigators
- The ability of participants' to withdraw information and/or specimens from the repository
- The types of information participants can expect to receive from the investigators and a clear delineation of the circumstances under which researchers will and will not attempt to re-contact participants
- The potential for commercial profit by the institution, investigator or sponsor from information gathered in the research and any plans for participants to share in commercial profits
- Procedures for protecting the privacy of participants and maintaining the confidentiality of the data and/or specimens

The informed consent form should also include a place for participants to indicate the following:

- Their individual preferences relating to the use of their data and/or tissue specimens
- Their decision regarding being re-contacted by the investigator with the results of the research tests if identifiable data and/or tissues are provided
- Measures taken to protect confidentiality

If tissue banking for future research is part of a clinical study, participants must be given the option to refuse participation in the tissue-banking portion of the study.

Specimens and data maintained in a repository may only be released to collaborators who are both qualified researchers and knowledgeable in the legal and ethical issues involved in confidentiality, consent and authorization in human participant research, regardless of where the investigators are located.

Data and/or specimens from UP or COM/PSHMC repositories are not provided to non-PSU investigators without written documentation of local IRB review and approval or documentation from the local IRB indicating that the study is exempt from IRB oversight. A written usage agreement for non-PSU investigator recipients must include a statement acknowledging the conditions for use as governed by the repository IRB and privacy requirements. Depending on the nature of the information that is released with

the data and/or specimen, a data use agreement or business associate agreement may be required. The IRB approval indicates if one of these additional agreements is necessary. Use of data and/or specimens from a repository is restricted to the stipulations indicated in the original consent/authorization form used to procure the data and/or specimen, unless the sample is studied without identifiers.

Investigators must obtain IRB review and approval when data and/or specimens from repositories will be studied at UP or COM/PSHMC or when UP or COM/PSHMC personnel are co-investigators, regardless of the location of the repository. IRB review and approval must be complete before the data and/or specimens are released for use. Investigators and repositories must maintain records to assure compliance with any specified restrictions of data and/or specimen use, including any restrictions placed by the person providing the data and/or specimen. Investigators receiving data and/or specimens with identifiers or codes are legally and ethically responsible for maintaining the confidentiality of the participants and for complying with all HIPAA requirements.

D. Genetic Research

Genetic research is defined as research involving the study of inherited human traits using human samples, genetic testing, and/or genetic information. Genetic research studies may create special risks to human participants and their relatives, including medical, psychosocial and economic risks, such as the possible loss of privacy, insurability and employability and risks associated with knowledge of one's genetic make-up and potential disease risk status of family members. Therefore, genetic information must be carefully maintained in order to protect against stigmatization, discrimination or significant psychological harm to the participant. During review of genetic research involving the collection of identifiable private information regarding third parties, IRB members will ensure that informed consent of the third party is obtained or waived as long as the research is not subject to FDA regulation and 45 CFR 46.116(d) is met.

IRB review considers the following issues, when applicable, in both the application and the informed consent document:

- What information can be obtained from DNA samples or genetic information in general, and the specific questions to be addressed in the study
- The extent of participant and sample confidentiality if the sample and the subsequent information will be part of a registry or database
- Plans to recruit and include other family members in the research
- The rights and limitations of participants to require destruction of their sample and/or associated data at a future date or to require that their sample and/or associated data be stripped of any identifying information
- Identifying information available to other researchers if their sample and/or associated data are part of a registry or database
- Measures to protect the research findings from third parties
- Mechanisms for maintaining confidentiality in long-term studies, registries, or databases
- To ensure maximum privacy, the IRB may require or recommend that a Certificate of Confidentiality be obtained from the Department of Health and Human Services
- The potential for commercial profit by the institution, investigator or sponsor from information gathered in the research and any plans for participants to share in commercial profits
- Plans for disclosure of information, including interim or inconclusive research results to participants

- The availability or access to genetic counseling in cases where a study may reveal genetically important information (i.e., possessing genetic defects which could be passed on)
- If genetic information will be disclosed to the participant or another party, the investigator disclosing the information must be named and the specific genetic information being disclosed must be stated
- Information disclosed must be in a manner consistent with the recipient's level of knowledge
- Participants must have the right to decline receiving genetic information
- Research results should not be given to any of the participant's family members or physician without the explicit, written permission of the participant
- The informed consent form should include any additional risks associated with the disclosure of the results of the genetic analysis, such as psychological, social and economic risks
- In the absence of a specific authorization to maintain a DNA sample, DNA samples collected and stored or analyzed in connection with a research study shall be destroyed upon completion of the study or withdrawal of the participant from the study. This information must be clearly stated in the informed consent document.

Before involving children in genetic research, the parent(s) or legal guardian(s) must review and sign the informed consent form. The informed consent form must give parents/guardians the option of whether or not they want the results (if available) of the genetic analysis disclosed to them. The IRB should consider whether the child has attained sufficient capacity for understanding the research and whether his/her assent is solicited. Unless the research holds a high probability of benefiting the participants directly, a child should not be forced to participate by any person against his/her wishes. Principal investigators must follow the appropriate measures with regard to releasing results of genetic research to children (e.g., counseling). Results should not be entered into the medical record unless they are relevant to the child's immediate medical care. In some genetic research studies, it may be possible to determine that some members of the family are not genetic relatives. Issues of genetic relationships (such as paternity or maternity), and other incidental information should not be disclosed. When exceptions to this requirement would be appropriate, justification should be provided in the research study.

XVI. POTENTIALLY VULNERABLE PARTICIPANT GROUPS

Certain groups of human participants are considered particularly vulnerable in a research setting. Federal regulations for protecting human participants in research include specific protections for children, pregnant women, human fetuses, neonates and prisoners. In reviewing these research studies, the IRB ascertains that the inclusion of the vulnerable population is adequately justified and that safeguards are implemented to minimize risks unique to each population. In addition, the PSU IRBs expect the principal investigator to provide additional safeguards for cognitively impaired individuals enrolled in research.

Each research study is evaluated for possible vulnerable populations. If a population is identified for which specific IRB policies and procedures do not exist, e.g. economically disadvantaged, terminally ill or employees, the IRB addresses the recruitment process and the consent process to determine if additional safeguards are required.

Approval for research studies involving vulnerable populations is considered if one of the following conditions is met: (1) the research does not involve more than minimal risk to the participant; (2) the research is likely to benefit the participant directly, even though the risks are considered to be more than minimal; or (3) the research involves greater than minimal risk with no prospect of direct benefit to

individual participants, but is likely to yield generalizable knowledge about the participant's disorder or condition.

A. Research Involving Children

Penn State adheres to the regulatory requirements for research with children, as outlined in 45 CFR 46 Subpart D, "Additional DHHS Protections for Children Involved as Participants in Research" and 21 CFR 50 Subpart D "Additional Safeguards for Children in Clinical Investigations." When reviewing research with children, the IRB membership includes at least one member who is knowledgeable about or experienced in working with children.

Federal law defines "children" 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. Under Pennsylvania law, persons under the age of eighteen (18) generally meet this definition of "children", with the exceptions noted below. As a result, permission of the child's parent(s) or guardian(s) must generally be obtained prior to the participation of that child in research. The following exceptions to the general rule apply, where a person under the age of 18 does not meet the federal definition of "child" and may provide legally effective consent to participate in research if either:

1. The research involves the provision of medical care or treatment, (including care or treatment deemed to be experimental) AND the person:
    a. has graduated from high school, or
    b. is married, or
    c. is or has been pregnant.
2. The person is an emancipated minor.

If an emancipated minor provides consent for himself or herself, the court order should be copied and included in the research records with the consent document.

As mentioned above, a child's "guardian" may provide legally effective consent for participation in research. Under federal law guardian means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. Except for research involving no greater than minimal risk, if a guardian provides consent, the court order or legal authorization to consent to general medical care should be copied and included in the research records with the consent document.

Children who are wards of the state or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406 and 45 CFR 46.407 or 21 CFR 50.53 and 21 CFR 50.54 only if such research is: (1) related to their status as wards; or (2) conducted in schools, camps, hospitals, institutions, or similar setting in which the majority of children involved as participants are not wards (45 CFR 46.409 or 21 CFR 50.56). Under the laws of the Commonwealth of Pennsylvania, neither foster parents nor Children and Youth Services can consent on behalf of a child for general medical care. Therefore they do not meet the federal definition of "guardian" and cannot provide consent for the participation of a foster child in a research study. Only the birth or adoptive parent(s) can provide the legally effective consent necessary.

If the research includes enrollment of participants in other states or countries, the principal investigator is responsible for providing the IRB with sufficient information to verify the age at which participants in such jurisdictions have the ability to consent to participation in research, including any medical treatments

or procedures if applicable. The IRB may, if it appears advisable, require the submission of an opinion rendered by an attorney from any applicable jurisdiction on age at which an individual can consent to participation in research.

The IRB reviews all research involving children as participants and approves only research that satisfies all the conditions of applicable subpart sections. The IRB assesses the potential risks and benefits for each research proposal, and the provisions for permission and assent, to determine if an activity satisfies the conditions for a category of research permitted in children, as specified in DHHS 45 CFR 46.404, 46.405, 46.406 46.407 and 46.409, and FDA 21 CFR 50.51, 50.52, 50.53, 50.54 and 50.56. The research categories are described below.

1. Research that does not involve greater than minimal risk may be approved if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians (45 CFR 46.404 and 21 CFR 50.51).

   For such research, the IRB determines whether adequate provisions have been made to solicit the permission of each child's parents or guardian unless one parent is deceased, unknown, incompetent, not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child. Where parental permission must be obtained, the IRB may determine that the permission of one parent is sufficient.

2. Research involving greater than minimal risk, but presenting the prospect of direct benefit to an individual participant, or a monitoring procedure that is likely to contribute to the participant's well-being, may be approved if the IRB finds that (45 CFR 46.405 and 21 CFR 50.52):
   a. the risk is justified by the anticipated benefit to the participant;
   b. the relationship of anticipated benefit to risk is at least as favorable as that presented by available alternative approaches; and
   c. adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

   For such research, the IRB determines whether adequate provisions have been made to solicit the permission of each child's parents or guardian, unless one parent is deceased, unknown, incompetent, not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child. Where parental permission must be obtained, the IRB may determine that the permission of one parent is sufficient.

3. Research involving greater than minimal risk with no prospect of direct benefit to individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition, may be approved if the IRB finds that (45 CFR 46.406 and 21 CFR 50.53):
   a. the risk represents a minor increase over minimal risk;
   b. the intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   c. the intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for the understanding or amelioration of the participant's disorder or condition; and

d. adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

For such research, the IRB requires the permission of both parents, unless one parent is deceased, unknown, incompetent, not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

4. Research that is not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children may be approved if the IRB and the Secretary of the Department of Health and Human Services (DHHS), after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, find that (45 CFR 46.407 and 21 CFR 50.54):
   a. the research in fact satisfies one of the above three conditions; or
   b. the following:
      i. research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
      ii. the research will be conducted in accordance with sound ethical principles; and
      iii. adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

   For such research, the IRB requires the permission of both parents, unless one parent is deceased, unknown, incompetent, not reasonably available, or unless only one parent has legal responsibility for the care and custody of the child.

If the IRB determines that the permission of both parents is required, permission granted by one parent will nevertheless be sufficient if the other parent is deceased, unknown, incompetent, not reasonably available or if the parent granting permission has legal responsibility for the care and custody of the child. In order to establish that only one parent has legal responsibility for care and custody of a child, an order issued by a court from the state in which such parent resides must grant sole custody of the child to such parent. A copy of the court order should be retained with the documentation of the parent's permission.

Assent is defined as "a child's affirmative agreement to participate in research." Passive resignation to submit to an intervention or procedure is not considered assent. Federal regulations do not specify any of the elements of informed assent and do not provide an age at which assent ought to be possible. In determining whether children are capable of assenting, the IRB takes into account the ages, maturity, and psychological state of the children involved. The IRB determines whether all or some of the children are capable of assenting. In general, capacity to assent is assumed to begin at about age seven. At COM, when the IRB determines that documentation of assent to participate in research is necessary, a child's assent signature statement will be required with the parental permission documentation for informed consent. For UP, IRB Guideline I "Obtaining Parental Consent and Child Assent," outlines specific information pertaining to obtaining and documenting assent from children.

The assent of the children is not a necessary condition for proceeding with the research if the IRB determines that the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

Investigators must obtain informed consent to continue in the research from participants who were enrolled as children but have now reached the age of majority. This consent to continue in the research must be documented by having participants sign a consent form for continued participation at the next study or clinic visit after becoming the official, legal consent authority for themselves. If participants are undergoing any research procedures or interventions, a current, approved version of the consent form must be used. If, however, all research procedures and interventions have been completed and the participant is in long-term follow-up involving data collection only, an addendum to consent for continued data collection may be used following IRB review and approval.

B. Research Involving Prisoners

The PSU IRBs comply with the requirements of 45 CFR 46, Subpart C, "Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Participants." The term "prisoner" refers to any individual: (1) involuntarily confined or detained in a penal institution; (2) sentenced under a criminal or civil statue; (3) detained in other facilities by virtue of statues or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution; and (4) detained pending arraignment, trial or sentencing. The same regulations that apply to prisoner enrollment in human participant research studies also apply to participants already enrolled in a study who suddenly become incarcerated. Moreover, federal regulations do not differentiate between detention, jail or prison. People incarcerated in any of these places are considered prisoners.

The principal investigator indicates in the application and provides justification to the IRB if the enrollment of prisoners is anticipated. If the study is not initially approved to recruit prisoners, the investigator may not enroll a prisoner. For ongoing research studies, investigators must notify the IRB immediately upon becoming aware of a current participant's incarceration, and all interactions, interventions and collection of protected health information (PHI) cease until requirements of Subpart C have been satisfied for the research. **EXCEPTION:** The principal investigator may assert to the IRB that it is in the best interest of the participant to remain in the research while incarcerated and the IRB Chair may determine that the participant may continue while the requirements of Subpart C are satisfied.

For review of research with prisoners:

- The IRB membership includes an individual with appropriate background and experience to serve as a prisoner representative, by nature of having experience or a close working knowledge, understanding and appreciation of prison conditions from the perspective of the prisoner. In addition, the majority of the IRB membership (exclusive of prisoner members) has no association with the prison(s) involved, apart from their membership on the board.

- When the IRB reviews research involving prisoners, the prisoner or prisoner representative is present as a voting member.

- The prisoner representative is present during the review of initial applications, continuing reviews, modifications, problem reports, and other reviews that may be applicable.

- An expedited review process can be used if appropriate to the research and the protocol meets all applicability criteria and involves procedures in one or more categories for expedited research. If the expedited review process is used to review research involving prisoners, the prisoner representative of the IRB must be one of the designated reviewers. OHRP recommends that a convened IRB review research involving prisoners as human participants.

- Exempt review does not apply to research with prisoners.

- Research involving prisoners is permissible only if the research involves one or more of four permissible categories, or if the research meets the criteria described in the Health and Human Services (HHS) Secretarial waiver that applies to certain epidemiological research [Fed. Register, Vol. 68, No. 119, 36929-31, 6/20/2003.]:

  - **Category A:** Studies of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;

  - **Category B:** Studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants;

  - **Category C:** Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary of the Department of Health & Human Services (DHHS) has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research; or

  - **Category D:** Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the participant. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary of DHHS has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of the intent to approve such research.

  - **The HHS Secretarial waiver for certain epidemiological research:** Research that involves epidemiologic studies that meet the following criteria: (1) The sole purposes are (i) to describe the prevalence or incidence of a disease by identifying all cases; or (ii) to study potential risk factor associations for a disease; and (2) where the research presents no more than minimal risk and no more than inconvenience to the prisoner-participants; and (3) prisoners are not a particular focus of the research; and (4) the required IRB findings under 45 CFR 46.305(a)(2)-(7) are met. [Fed. Register, Vol. 68, No. 119, 36929-31, 6/20/2003.]

- In addition to the other responsibilities described in the section for research involving prisoners, the IRB can only approve research studies if it finds that:
  1. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

2. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;

3. Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides a written justification for following some other procedures to the IRB, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research study;

4. The information is presented in a language and reading level that is understandable to the participant population;

5. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

6. Where the IRB finds a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care taking into account the varying lengths of individual prisoners' sentences and for informing participants of this fact.

- If a study utilizing prisoners as research participants is federally funded, the ORP/HSPO must send a letter to the Office for Human Research Protections (OHRP) indicating it has approved a study that will include prisoners, the category the study fits into as well as how the study satisfies the six criteria listed above. A research study is not permitted to commence for DHHS supported research until written approval is received from OHRP on behalf of the DHHS Secretary.

- If a study utilizes prisoners from a state prison in Pennsylvania, the investigator must submit a Research Approval Request Form (RARF) to the Pennsylvania Department of Corrections for review and approval. The RARF and a copy of the approval letter from the PA Department of Corrections must be submitted to the IRB along with the application and supporting documents for review and approval by Penn State's IRB.

C. Research Involving Pregnant Women, Fetuses, In Vitro Fertilization, Neonates

Penn State adheres to the regulatory requirements of 45 CFR 46 Subpart B, "Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research." Pregnant women or fetuses may be involved in research only if the conditions outlined in the regulations are met including scientific appropriateness, acceptability of potential risks and benefits, compliance with the additional informed consent provisions, absence of any inducements (monetary or otherwise) to terminate a pregnancy, and confirmation of the independence of the researchers from the decisions related to pregnancy termination and/or any decisions related to the determination of viability of a neonate.

For research involving the transplantation of fetal tissue, the IRB will also follow the regulatory requirements of 42 USC §498A, "Research on Transplantation of Fetal Tissue." These requirements include specific conditions that must be met along with the written acknowledgement required from the woman donating fetal tissue for research, the physician obtaining the donated tissue, and the researcher

who will use the tissue. The stipulations relate to the circumstances of the donation and the uses including the requirement that there be no restrictions regarding identities of the recipients of the tissue for transplantations; no alteration in the timing, method, or procedures used to terminate the pregnancy for the purposes of obtaining the tissue; and that there be independence regarding any decision for an abortion from the consent for donation of tissue. Also, there must be full disclosure to the woman regarding the physician's interest, if any, in the research to be conducted with the tissue; full disclosure of any known medical risks to the woman or to her privacy associated with the donation; and confirmation of awareness by the involved parties that the tissue is human fetal tissue and that it may have been obtained pursuant to a spontaneous or induced abortion or stillbirth.

D. Research Involving Persons with Decisional Impairment

Although the Department of Health and Human Services (DHHS) does not provide additional regulations for research involving persons with decisional impairment, PSU IRBs require that additional safeguards be included in research to protect the rights and welfare of these participants.

The PSU IRBs have to specifically authorize the enrollment of adults with decisional impairment. If the research was not initially approved to recruit decisionally impaired persons, then the investigator may not enroll these individuals unless the investigator submits a study modification request to the IRB for authorization to enroll persons with decisional impairment. If a research study is authorized by the IRB to enroll decisionally impaired persons, participants are recruited from among non-institutionalized populations whenever possible. Investigators will need to provide justification for enrolling institutionalized adults with decisional impairment (e.g., the research pertains to aspects of institutionalization and/or non-institutionalized individuals are not appropriate for the research or reasonably available). For research involving treatment of persons undergoing mental health treatment within a Pennsylvania-based mental health facility, the research study must be approved by Pennsylvania's Deputy Secretary of Mental Health.

Limited decision-making capacity or decisional impairment are used to refer to adults who may have one or more of the following types of limitations:

- Fluctuating decisional impairment, e.g., schizophrenia, bipolar disorders, depressive disorders, delirium, and some dementias
- Progressive decisional impairment, e.g., persons for whom decision-making deficits can be predicted due to the course of their disease or the nature of their treatment. Although these individuals may be decisionally capable in the early stages of the disease progression, such as Alzheimer's disease or other forms of dementia, they have prospective incapacity
- Limited decisional impairment, e.g., persons with limited capacity but who are still able to object or assent to research, as in the case of stroke, more advanced Alzheimer's disease, or developmental disability resulting in cognitive impairment
- Complete decisional impairment, e.g., persons who have lost the ability to make decisions that involve significant reflection, as in the later stages of Alzheimer's disease or unconsciousness due to trauma or a medical treatment (sedation) or illness

Research involving persons with decisional impairment are limited to the following three categories:

- **Category 1:** Research presenting no greater than minimal risk to the involved participants.

- **Category 2:** Research involving an intervention or procedure that presents an increase over minimal risk to involved participants, but which offers the potential for direct individual benefit to the participant and is available only in the context of the research study.

- **Category 3:** Research involving an intervention or procedure that presents an increase over minimal risk to involved participants and that does not have the potential for direct individual benefit provided that the knowledge sought has direct relevance for understanding or eventually alleviating the participants' disorder or condition.

Studies involving high risk or studies involving greater than minimal risk with no potential for direct individual benefit and no direct relevance for the disorder or condition causing the impairment will generally not be approved.

For new research studies, the principal investigator must provide:

- Justification and category designated for the research being conducted
- When it will be necessary to obtain informed consent from the participant's legally authorized representative along with the following additional information:
  - The rationale for the need to obtain consent from a legally authorized representative
  - The criteria used in determining whether a potential participant has a decisional impairment sufficient to require the use of consent from a legally authorized representative including any use of standardized assessment tools
  - Who will conduct the assessment
  - The additional safeguards used to protect the rights and welfare of the participants
  - The additional methods proposed to enhance participants' ability to achieve decisional capacity with regards to the proposed study
  - The process for obtaining consent from a legally authorized representative
  - The process for obtaining and documenting assent unless a waiver of assent is requested
- When the investigators plan to recruit institutionalized adults with decisional impairment, justification for using this population is required

For ongoing research studies not initially requesting IRB approval to enroll decisionally impaired persons, investigators must notify the IRB in writing immediately upon becoming aware of a potential participant with decisional impairment. At that time, the IRB determines if the research may be approved to enroll individuals who have impaired decisional capacity.

For review of research involving persons with decisional impairment, the IRB may involve consultant(s) who is familiar with the nature of the disorder(s) and with the concerns of the population being studied in this discussion.

The IRB also may employ the following additional safeguards where appropriate:

- An independent party (independent of the study investigator with appropriate expertise) to assess the capacity of a potential participant
- Standardized assessments of cognition and/or decisional capacity
- An independent monitor to observe the recruitment, assessment and the informed consent process
- Informational or educational techniques to assess and enhance comprehension at each stage of the research. Tools to aid in this effort may include single sheet summaries of important information

about key elements of the studies, regular opportunities for study participants and their families to ask questions, and other educational tools to enhance understanding, including use of videos demonstrating study interventions or use of post-tests documenting comprehension
- Waiting periods. Vulnerable populations may need additional time to consider information about a research study. Planning built-in periods into the informed consent process may be useful to increase comprehension in decisionally impaired populations and to allow involvement of participants' family members, where appropriate
- Consent from a legally authorized representative
- Assent, in addition to consent from a legally authorized representative, in order to respect the autonomy of individuals with decisional impairment

As a general rule, all adults, regardless of their diagnosis or condition, are presumed competent to consent to participate in research unless there is evidence of a serious disability that would impair reasoning or judgment. When investigators propose to include individuals with questionable capacity, the investigators must provide a plan for assessing the participants' decision-making capacity. Assessment is done on an individual basis and should determine the potential participants' ability to understand and express a reasoned choice based on:

- The voluntary nature of research participation and the information relevant to his/her participation (research procedures);
- Consequences of participation for the participant's own situation, especially with regard to the participant's health condition;
- Consequences of the alternatives to participation;
- Potential risks and benefits involved in the study; and
- Procedures to follow if he/she experience discomfort or wishes to withdraw.

If the assessment shows evidence that the participant is competent to consent, the investigators obtain valid informed consent directly from the participant. If the assessment determines that the potential participant does not have sufficient capacity to consent, the investigator must do the following:

- Document the participant is incapable of understanding the information presented regarding the research in the participant's research record;
- Document the information provided to the participant's legally authorized representative regarding the cognitive and health status of the participant, the risks and benefits of the research, and the role of the legally authorized representative in the research record;
- Obtain the consent and signature of the participant's legally authorized representative; and
- Obtain and document the participant's assent if the person with decisional impairment is capable of exercising some judgment concerning the nature of the research.

The verbal objection of an adult with decisional impairment is binding. If the participant, at any time, objects to continuing in the research study, he/she cannot participate in the research study. Situations may arise in which the investigator could legitimately return to the participant at a later point to ascertain whether the previous objection still stands. The only exception will be research providing direct benefit only available in the context of the research, in which case the investigator must submit a request to the IRB to enroll or continue the participant and provide written documentation of the agreement of the participant's legally authorized representative. In this instance, the IRB may solicit advice of experts.

When appropriate, the consent process may be altered to allow for non-verbal or other alternative consent methods. Proposed alterations to the consent process are submitted for IRB review and approval.

Consent by a Legally Authorized Representative

Under federal law "legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the individual's participation in the procedure(s) involved in the research. When research is conducted in Pennsylvania, the following individuals are authorized under Pennsylvania law to consent on behalf of a prospective participant to the individual's participation in the procedure(s) involved in the research, and therefore meet the federal definition of "legally authorized representative":

- Court-appointed legal guardian: If the potential participant has been declared legally incapacitated by a court, a guardian of that person should have been appointed. In this instance, the court-appointed guardian is the only individual who may serve as a legally authorized representative, provided however, the court order must specifically grant the guardian the authority to consent to participation in research. Without such express authority, even the court-appointed guardian may not serve as a legally authorized representative.

- Health Care Power of Attorney: Where a potential participant has executed a valid Health Care Power of Attorney ("DPAHC"), the person named therein may serve as a legally authorized representative for participation in research that involves medical care or treatment which has the potential to provide a direct benefit to the participant.

- Health Care Representative: Typically, potential research participants have neither a court-appointed guardian nor a DPAHC. In such cases, legally effective consent may be provided on behalf of the decisionally impaired adult by an individual involved in the patient's care, called a "health care representative". Such individuals may provide the necessary consent for adult patients who have no controlling will, no health care agent under a Power of Attorney, and no legal guardian of the person. Health care representatives are designated either by the patient or by a pre-determined priority list, and generally have the same broad authority as may be given to a health care agent. The priory list for a health care representative is:
    1. Current spouse and adult child who is not the child of the current spouse
    2. Adult child
    3. Parent
    4. Adult sibling
    5. Adult grandchild
    6. Close friend

If the highest priority person is not reasonably available, the person of next highest priority may be used. Legally effective consent may be obtained by a health care representative for participation in research that involves medical care or treatment that has the potential to provide a direct benefit to the participant.

If the research will involve enrollment of persons with decisional impairment in another state or country, the principal investigator is responsible for providing the IRB with sufficient information to verify the legally authorized individuals who may provide substituted consent within such jurisdictions. The IRB may, if it appears advisable, require the submission of an opinion rendered by an attorney from any

applicable jurisdiction as to which persons are legally authorized to consent to participation in research on behalf of a decisionally impaired participant.

The legally authorized representative should be informed about the study, its implications for the individual, and the representative's role in providing initial and ongoing consent. The representative should be informed of all risks, benefits and alternatives to the medical treatment provided as part of the research protocol, just as any other participant would be. Further, such consent should reflect, whenever possible, the views and beliefs the participant had prior to his or her decisional impairment. This is called "substituted judgment". If the participant's preferences are unknown, decisions may be based on the participant's inferred preferences based on a long-standing and close relationship with the legally authorized representative. If the legally authorized representative is not confident of the participant's inferred preferences, a decision must be based on what is in the participant's best interest.

Where the condition causing the participant's decisional impairment is of an intermittent or temporary nature, the informed consent process should include a mechanism for obtaining the participant's subsequent direct informed consent to participate in the research. If such a participant, upon regaining decisional capacity, or at any time declines to continue participation in the research, such a decision is honored. When the participant regains decisional capacity, he or she must be informed of his/her enrollment in the research and, if the research is ongoing, given the opportunity to continue participation or withdraw from the study.

The investigator uses the "Notice of Participation" form to document this discussion and the decision of the participant to consent or decline continued participation in the research. If the participant chooses to continue the research, an informed consent process is conducted using the current approved written informed consent form for participation.

If a legally authorized representative cannot be identified, an individual with decisional impairment cannot be enrolled in research unless the IRB has waived the requirement for consent.

XVII. MANAGEMENT OF FDA REGULATED RESEARCH

The U.S. Food and Drug Administration (FDA) regulates clinical studies conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements and food additives, hereinafter referred to as "FDA regulated test articles." All such research studies must be conducted in accordance with FDA requirements for protection of human participants and IRBs, regardless of funding (21 CFR Parts 50 and 56).

When FDA regulated test articles are used in research being conducted at PSU or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by the Department of Health and Human Services (DHHS) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human participant regulations. Where regulations differ, PSU and COM IRBs will apply the stricter one.

A. IRB Review of Medical Devices

The PSU IRBs will comply with the requirements of 21 CFR Part 812. These regulations permit IRBs to approve a research study involving investigational devices after differentiating between significant risk (SR) and non-significant (NSR) devices. A SR device must have an investigational device exemption (IDE) number from the FDA, while a NSR device does not. Thus, if a clinical research study is submitted to the IRB for a device that has an IDE, the device is considered a SR device.

A SR device means an investigational device that:

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

A NSR device is an investigational device that does not meet the definition of a SR device. The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses SR, the IRB considers the nature of the harm that may result from the use of the device. Studies where the potential harm to participants could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure are considered SR studies. Also, if the participant must undergo a procedure as part of the investigational study (e.g., a surgical procedure), the IRB considers the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

Because NSR studies are considered to have an IDE, a clinical investigation involving an investigational device classified by the sponsor as NSR may be submitted to the IRB for review without an IDE number issued by the FDA. With this type of research, the IRB must determine whether the device involves significant risk or non-significant risk to participants. To help in the determination of the risk status of the device, the investigator provides the IRB with the following:

- Sponsor's (including the investigator's on investigator-initiated studies) risk assessment and the rationale used in making its NSR risk determination
- Device description
- Reports of prior investigations with the device
- Proposed investigational plan
- Participant selection criteria description
- Monitoring procedures
- Determinations made by other IRBs
- FDA's assessment of the device's risk, if such an assessment has been made

The IRB must review the information and makes its own independent determination of risk. The IRB may agree or disagree with the investigator/sponsor's initial NSR assessment and/or may consult with the FDA. If the IRB determines that the study involves a SR device and disagrees with the assessment of the sponsor, the IRB notifies the investigator and the sponsor of this decision. The sponsor notifies the FDA

that an SR determination has been made and submits an IDE application to the FDA. The FDA has the ultimate decision in determining if a device is SR or NSR. The study cannot begin until the FDA approves the IDE and the IRB approves the study. The IRB must be provided with notice that an IDE has been granted. The IDE number must appear on the investigator's IRB application prior to final convened IRB review. The investigator/sponsor must provide one of the following to document the IDE number: (1) a letter from the FDA (required when the investigator is the sponsor); (2) a face sheet from the sponsor's protocol; or (3) correspondence from the sponsor.

If the IRB determines that the device is classified as NSR (concurs with the assessment of the sponsor) and approves the study, the clinical research may begin without the submission of an IDE application to the FDA. Once the SR/NSR decision has been reached and proper documentation provided, the IRB considers whether the study should be approved or not. Convened IRB review is required for all studies involving investigational devices. The criteria for approving the clinical research study are the same as for all other studies. IRB meeting minutes document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

B. IRB Review of Research Involving Drugs and Biological Products

The PSU IRBs will comply with the requirements of 21 CFR Parts 312 and 600 for the review and approval of research studies involving FDA regulated drugs and biological products.

- Studies that involve FDA regulated drugs or biologics that are submitted without a valid investigational new drug (IND) number are reviewed with respect to determining the need for an IND, based on the investigator's response to questions contained in the research application. If the IRB determines that the study is exempt from an IND and approves the study, the study may begin without submission of an IND application to FDA. If the IRB determines that an IND is needed, the investigator/sponsor must submit an IND application to the FDA and provide one of the following to document the IND number: (1) a letter from the FDA (required when the investigator is the sponsor; (2) a face sheet from the sponsor's protocol; or (3) correspondence from the sponsor.

The IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

- The research study is not intended to support a new indication for use nor any other significant change in the labeling for the drug;
- The research study is not intended to support a significant change in the advertising of the product;
- The research study does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The research is conducted in compliance with the requirements for institutional review and informed consent; and
- The research study is conducted in compliance with the FDA regulations with regard to promotion and charging for investigational drugs.

Use of an off-label marketed product in research intended to support a new indication for use, change in labeling or advertising requires IRB review and approval, informed consent and submission of an IND.

A clinical research study involving an in vitro diagnostic biological product that is a blood grouping serum, reagent red blood cells, or anti-human globulin is exempt from the requirements for an IND if: (1)

it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (2) it is shipped in compliance with 21 CFR 312.160. A drug intended solely for tests in vitro is exempt from the requirements of an IND if it is shipped in accordance with 21 CFR 312.160. A clinical research study involving the use of a placebo is exempt from the requirements of an IND if the research does not otherwise require submission of an IND.

C. Emergency Use of an Investigational Drug/Device

An exemption under FDA regulations (21 CFR 56.104) permits the emergency use of an investigational test article without prior IRB review and approval. Emergency use is defined as a life-threatening situation in which: (1) no standard acceptable treatment is available and (2) there is not sufficient time to obtain IRB approval. Whenever possible, it is the responsibility of the investigator to consult the IRB Chair for guidance prior to any emergency use of a test article. The investigator must obtain the informed consent of the participant for such an emergency use, unless the emergency situation does not make it feasible to obtain informed consent prior to using the test article. The emergency use must be reported to the IRB in writing within five working days. For specific information on the IRB policy for emergency use of an investigational drug/device, see the "IRB SOP Addendum: Research Activities in Emergency Situations".

D. Treatment Use of an Investigational Drug/Device

A treatment IND/IDE is a mechanism for providing investigational drugs or devices to eligible patients for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. The IRB reviews the use of the investigational drug/device if the investigator provides evidence that a treatment IND/IDE has been obtained from the FDA. In all cases, treatment use of an investigational drug/device requires prospective IRB review and approval as well as participant informed consent.

E. Planned Emergency Research

An exception under FDA regulations (21 CFR 50.24) permits planned research in an emergency setting without the informed consent of participants or their legally authorized representatives. Planned emergency research that is not FDA-regulated is also permitted by DHHS.

The requirements for planned emergency research without informed consent are extremely complex and require consultation within this institution, within the community, and with the federal agencies involved. Investigators should contact the IRB Chair well in advance if they wish to conduct planned emergency research. It is the responsibility of the IRB Chair to provide prompt written notification to the institution's Institutional Official, Legal Counsel, and the ORP or HSPO should the IRB receive a proposal for planned emergency research.

For specific information on the IRB policy for planned emergency research, see the "IRB SOP Addendum: Research Activities in Emergency Situations".

F. IRB Review of Humanitarian Use Devices

A humanitarian use device (HUD) is a device that the FDA has determined is intended to benefit patients in the treatment and diagnosis of diseases/conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year. The use of a HUD within its approved labeling does not constitute research. The FDA, however, requires IRB review and approval before a HUD is used.

The PSU IRBs are responsible for initial as well as continuing review of the HUD. The initial review of a HUD is conducted by the convened IRB. The investigator is required to submit a new application for review. Included in the application must be evidence that the investigator/sponsor has obtained a Humanitarian Device Exemption (HDE) from the FDA, which authorizes marketing of a HUD. The investigator must also provide the participant information that will be used to assist a patient in making an informed decision about the use of the device. Although informed consent for the use of a HUD is not required by federal regulations, the IRB may determine that prospective informed consent is necessary. The IRB does not need to review and approve individual uses of a HUD. As long as the use of the HUD is within the FDA approved indication, the IRB may approve use of the device however it sees fit. For continuing review, the IRB may use the expedited review procedures unless the IRB determines that convened IRB review should be performed.

XVIII. MANAGING CONFLICTS OF INTEREST

Conflict of interest (COI), where a set of conditions in which judgment concerning a primary interest may be biased by a secondary interest, is inherent to the conduct of research. In any given situation, conflict of interest must be managed through a system of identification, disclosure, containment, reduction, and elimination.

PSU has the following policies that define conflict of interest and outline the requirements regarding COI at the institutional and individual level:

- Policy HR91 – "Conflict of Interest"
- Policy RA20 – "Individual Conflict of Interest"
- Policy RA21 – "Institutional Financial Conflict of Interest involving Sponsored Projects, Dedicated Gifts, Research Scholarship, and Technology Transfer"
- Guideline RAG20 – "Guidance on the Disclosure of Significant Financial or Business Interest(s)"
- In addition, PSCOM/HMC also complies with the policy, "Individual Conflict of Interest Oversight on the Penn State University College of Medicine/Milton S. Hershey Medical Center Campus".

Mechanisms to help maintain objectivity in IRB review of human participant research include: (1) excusal of members from the final deliberation and voting on studies in which they have declared a conflict of interest; (2) placement of the IRB within the institution in a position of independence to avoid undue influence and bias in reporting structures and policies; and (3) proactive education to increase awareness of existing policies regarding conflicts of interest.

A. Research Personnel

The IRB and the ORP/HSPO staff help investigators and research personnel to understand how COI can influence the protection of human participants. Activities include consulting with investigators and research personnel, sponsoring educational activities on conflicts of interest and disseminating information on PSU policies regarding conflict of interest disclosure and management requirements as well as institutional requirements.

The IRB requires that investigators and research personnel provide written information in the application regarding any COI relevant to research studies submitted for IRB review. To ensure that COI does not compromise the rights and welfare of human participants research, the IRB determines: (1) if methods used for management of financial interests of parties involved in the research adequately protect the rights

and welfare of human participants; (2) if other actions are necessary to minimize risks to participants; and (3) the kind, amount, level of detailed information to be provided to research participants regarding a conflict of interest and any management techniques applied.

In addition to the disclosures required to the COI committees, research investigators must disclose any conflicts of interest to the IRB:

- At the time of initial review by the IRB;
- At the time of application for continuation review; and
- When there are changes in financial circumstances that affect a research investigation

Investigators are responsible for informing the IRB of the existence and nature of the conflict of interest and COI management plan, in writing, within 30 days of disclosure to the COI committee.

If a conflict of interest is described in the human participant application, final approval is not granted until the IRB has reviewed the findings and recommendations of the COI Committee(s), described in Section F below. The IRB has final approval over whether the management plan adequately protects participants. Investigators are allowed to submit an application for IRB review; however, final IRB approval is not granted without review of the COI management plan. The IRB may accept the management plan or require additional management measures.

For research qualifying for exemption or expedited review, the designated reviewers will review the COIC or CIRC communication and findings and decide whether the conflicting interest and its management plan, if any, allow the research to be approved.

For research qualifying for convened review, the IRB will review the COIC communication and findings and decide whether the conflicting interest and its management plan, if any, allow the research to be approved.

- At UP, if a human participant research application indicates an individual conflict of interest exists, the IRB staff works with the COI Coordinator, who coordinates the COIC. A follow-up is placed in PRAMS indicating a COI management plan is needed for IRB review and approval. PRAMS will not allow studies to receive final approval if there are any follow-up due.

- At the COM, the IRB will review the details of the COI provided in the IRB application, and information available from CIRC, and decide whether the conflicting interest and its management plan, if any, allow the research to be approved. The CIRC has established conflict of interest review levels and guidelines for identifying categories of disclosures by their risk level and potential to create research bias or interfere with human participant protection. These guidelines, Research Conflict of Interest: Coordination with IRB Reviews, identifies anticipated actions for each review level, such as disclosure in the consent process or assignment of a research monitor. For disclosures of situations that involve minimal risk or pose a low to intermediate potential for bias or interference, these studies may undergo IRB review prior to the CIRC, provided that approval is <u>not</u> be granted until after the CIRC review has been completed. In these cases, if other guidelines are recommended by the CIRC, in addition to the anticipated actions outlined, the study will require re-review by the convened IRB. For disclosures of situations that meet a category deemed to involve high potential to create research bias or interfere with human participant protection, the IRB review will be deferred until <u>after</u> the CIRC has been completed.

B. IRB Members

No IRB member may participate in the initial review, continuing reviews or modification requests, problem reports or non-compliance reviews for any research study in which the member has a conflict of interest (COI), except to provide information requested by the IRB.

IRB members are automatically considered to have a conflict of interest if they, their spouses, or any dependent children:

- are involved as research personnel on the study under review; or
- have a significant financial or business interest in the research as defined in PSU Policy RA20, "Individual Conflict of Interest".

IRB Member Disclosure

IRB members are required to complete an "IRB Member Conflict of Interest Disclosure Agreement" upon appointment to the IRB and sign an updated agreement annually.

IRB members are required to disclose the existence of any conflict of interest they may have related to the research under review. When conducting a primary or secondary review, IRB members are required to sign a reviewer's checklist attesting that they do not have a conflict of interest.

Expedited review: For expedited reviews, IRB members must immediately inform the IRB staff of the existence of conflicts of interest regarding an expedited study that is assigned to him/her for review. The member may not review the study but must return it for re-assignment to another reviewer.

Convened review: For convened meetings, IRB members are reminded of the COI policy at the start of each board meeting and instructed to disclose the existence of any COI prior to the beginning of the IRB's discussion of the research in which the member has a conflict. An IRB member with a COI may only participate in the review to answer any questions for the board, but must absent him/herself from the room during the final deliberation and vote for any research in which the member has a conflict of interest. IRB members with a conflict are excluded from the quorum for the research study under review. The IRB minutes reflect by name all individuals excluded due to a COI. In cases where an assigned designated reviewer has a conflict of interest, the individual is required to inform the ORP/HSPO prior to the meeting and so the study may be reassigned to another reviewer. When an IRB Chair is excluded from the review for a particular study because of a conflict of interest, the Vice-Chair or a chair pro tem is appointed to lead the meeting during the review.

If there is a question about whether a situation represents a conflict of interest, the IRB member should disclose the matter and ask the IRB staff or the board to make a determination. The situation will be considered to constitute a conflict of interest by meeting either of the conditions described above.

Departmental and Employment Capacities

IRB members serving in a role for the study relative to their employment capacity for the institution, such as statistician or investigational pharmacist, are not considered as having a conflict of interest in and of the role itself. Such members are permitted to participate in the deliberation and vote on the research provided they have no other conflicting interest and will not have any responsibility that might influence the outcome of the research.

Working in the same department or division of an investigator for a proposed study is not considered, in and of itself, to be a conflict of interest. IRB members are permitted to vote on studies submitted by members of their own department or division because often they are the most knowledgeable about the topic being investigated but only if the IRB member has no other conflicting interest such as responsibility for the design and oversight of the study.

Management of Efforts to Influence IRB Review

IRB members who believe they have been involved in attempts by investigators or others to influence the review of a particular study bring the matter to the attention of the IRB Chair. The IRB Chair considers the substance of the matter and determines if the situation presents the potential to influence the member's review or for others to perceive that a conflict exists. If so, the member is advised to disclose to the board that a conflict of interest exists and to follow the COI exclusion requirements. If an IRB Chair has been subjected to attempts to influence the review for a particular study, he or she should ask the Vice-Chair or a chair pro temp to lead the review for that issue.

The IRB Chair, having reason to believe that a member of the faculty, staff, or a member of the student body has attempted undue influence of an IRB member, discusses the situation with the Senior Vice President for Research at University Park or the Vice Dean for Research at the College of Medicine who conducts an investigation. Allegations may be the result of misinterpreted communication or misunderstanding and therefore, they may be subject to resolution on a collegial basis through discussion(s) designed to ascertain whether there is reason to believe that research misconduct may have occurred. If the results of the discussion(s) confirm the possibility of research misconduct, the Senior Vice President for Research or Vice Dean for Research promptly provides the allegations in writing to the accused individual. The policy for research misconduct is followed.

C. Consultants and Guests of the IRB

Consultants

Consultants to the IRB must follow the same conflict of interest definition that applies to IRB members, outlined in the previous section. An HSPO/ORP staff member provides the consultant with a "Conflict of Interest Disclosure and Confidentiality Agreement" to complete and determine whether the individual has a conflicting interest. An individual with a conflict of interest related to a research study may not serve as a consultant for that study.

Guests

Individuals allowed to attend an IRB meeting as guests may observe only and may not participate in the meeting. Guests are required to follow the same definitions for conflict of interest that apply to IRB members, outlined in the previous section. Guests sign a statement agreeing to disclose to the IRB if they have a conflict of interest with regard to a specific research study under review and to excuse themselves before the final deliberation and vote for the particular research study (UP – "Convened IRB Meeting Guest Statement"). Completion of the guest statement is not required for investigators who attend the IRB meeting only during the review of their research to present information or answer any questions for the board, since they are automatically excused before the IRB begins the deliberation and vote on the research under review.

D. Institutional Officials

As academic institutions have increasingly entered into financial and collaborative research arrangements with private industry, institutional conflicts of interest have become a topic of growing concern and

increasing public scrutiny. To avoid the potential for COI, Institutional Officials do not serve as an IRB member unless a compelling situation exists.

E. Disclosure Process

For the purpose of preventing, monitoring, identifying, managing and resolving conflicts of interest, PSU requires full disclosure from investigators and research personnel, IRB members and Institutional Officials. Disclosure is made to the appropriate COI Committee, if applicable, and the appropriate IRB or IRB Chair. The IRB determines if disclosure to the human participants involved in the research may be warranted via the informed consent form along with other management measures.

F. Committees for the Review of Conflict of Interest

Individual Conflict of Interest Committees

An Individual Conflict of Interest Committee (COIC), who reports to the Provost or if the Provost is the one involved in the conflict, to the next highest University official who is not involved in the specific conflict, has been established to review significant financial or business interests that may compromise or have the appearance of compromising an employees judgment in research. The COIC membership represents the diversity of academic disciplines at Penn State and includes at least one individual who conducts research involving human participants at Penn State. The ORP Director, who serves as the Conflict of Interest Official (or delegate at the College of Medicine), will also act as the liaison to the University's IRBs.

As provided in PSU Policy RA20 “Individual Conflict of Interest”, the COI Official has delegated the responsibility of the day-to-day management of financial conflicts to the Vice Dean of Faculty and Administrative Affairs at COM/PSHMC. Oversight for conflicts of interest at the COM/PSHMC campus is provided by the Conflict of Interest Review Committee (CIRC). The membership is composed of faculty and staff representing the diversity of academic and research disciplines of COM/PSHMC. An IRB member, who is not a PSU faculty member, attends meetings of the CIRC as an *ex officio* member to represent the advocacy of the COM IRB for the interests of human participants.

The policies and responsibilities of the COIC and CIRC, outlined in PSU Policy RA20, include the following with respect to human subject protection:

- When human participants are involved, no de minimus will apply.
- If human participants are involved, determine whether the financial/business interest will adversely affect the protection of participants, whether the financial interest will adversely affect the integrity of the research, and when a financial/business interest may affect the protection of participants, indicate that disclosure to potential participants or the public cannot be used as the sole method of management.
- Communication to the IRB and to responsible Institutional Officials with summarized information about the nature and amount of any significant financial interests related to human participants in research, along with the committee's findings and recommendations concerning requests by financially interested individuals to conduct such research.

The COIC and CIRC review cases in which an investigator has disclosed significant financial interests that may impact research involvement. Management strategies, such as conflict disclosure, appointment of a monitor and/or disqualification of the investigator from participating in the study are developed and implemented to assure that the investigator may satisfy his/her research obligations in an objective manner and to avoid and/or mitigate concerns of bias.

Written information is provided to the IRB(s) and Institutional Officials of summary information about reports of individual financial interest in human participant research along with the Committee's findings.

Institutional Conflict of Interest Committee (ICIC)
An Institutional Conflict of Interest Committee (ICIC), who reports to the Office of the President, has been established to review disclosures that present or appear to present an institutional conflict of interest according to PSU Policy RA21, "Institutional Financial Conflict of Interest Involving Sponsored Projects, Dedicated Gifts, Research, Scholarship and Technology Transfer".

ICIC membership includes an officer of the University who has sufficient seniority, expertise, and independence to evaluate competing interests at stake and make credible and effective recommendations. Additional members include a COM representative, at least one faculty member, and at least one member of the community. Recusal is required whenever any member has an actual or apparent conflict of interest with regard to any matter under review. The ICIC includes one or more alternates to sit in place of any member who has recused him/herself from the deliberations. The ORP Director, who serves as the COI Official and the ICIC administrator, will also be the liaison to PSU's IRBs when human participant research is involved.

ICIC responsibility includes:

- Review of disclosures that present or appear to present an institutional conflict of interest.
- Development of conflict resolution plans.
- Documenting the committee's findings and the basis for the approval of conflict resolution plans, including steps to be taken to manage the conflict or minimize the potential for conflict of interest by reducing or eliminating the interest.
- Oversight of studies that are being managed with respect to conflicts of interest.

Written information is provided to the IRB(s) and responsible Institutional Officials of summary information about the nature and amount of the institutional financial interest in human participant research along with the Committee's findings. If a human participant research application indicates an institutional conflict of interest exists, the IRB staff works with the ORP Director, who coordinates the ICIC. A follow-up is placed in PRAMS indicating a COI management plan is needed for IRB review and approval. PRAMS will not allow studies to receive final approval if there are any follow-ups due.

XIX. EDUCATION AND TRAINING

A. Investigators and Research Personnel

All investigators and key research personnel involved with human participant research under the auspices of PSU must complete the minimum institutional requirements for education in human participant protection prior to participating in the conduct of research. This requires completion of a basic tutorial covering issues and ethical principles important to conducting human participant research, a review of the informed consent requirements, privacy and confidentiality issues for data and participant/patient records, assessment of risks and benefits, regulatory requirements for protecting human participants and the IRB review process.

The principal investigator is responsible for ensuring that he/she and the research staff successfully complete the basic tutorial and related quiz before beginning the research study. The proposed research study will not be approved until the basic education requirement is met by all key personnel.

Key Research Personnel are individuals who (1) are involved in the design and/or conduct of the research, (2) have access to human participants, and/or (3) have access to confidential *and* identifying information. This includes principal investigators, co-investigators (sub-investigators), research nurses, study/project coordinators, associates/assistants, students, advisors and other support staff or persons assisting with the research.

At UP, students who serve as a principal investigator on a research study are required to have a faculty member serve as his/her advisor. The advisor must be experienced in conducting human participant research and institutional requirements regarding human participant research. At COM, undergraduate or graduate students serving as first time principal investigators are expected to have an advisor experienced in human participant research and familiar with institutional requirements.

Basic Educational Requirements

At UP, investigators and research staff involved with human participant research complete the IRB's "Basic Training on the Protection of Human Participants" or provide verification of accepted training outlined in IRB Policy II, "Verification of Training on the Protection of Human Participants," located on the ORP website.".

At COM, investigators and research staff complete the internet-based CITI Course in The Protection of Human Research Subjects or provide certification of accepted training as outlined in the IRB procedure "Penn State Hershey Human Research Protection Education Requirement". The training requirement must be met for key research personnel in the convened or expedited categories and for exempt research activities if an activity will be used for a medical student research project. Additional training requirements for federally funded research will apply when applicable, such as NIH requirements. The COM requires continuing education in human research protection every three years. Certification of current training completion for all investigators and key personnel will be verified by the IRB Coordinator at the time of each new submission. New research proposals for convened IRB review will be placed on an IRB agenda only after the principal investigator has met the current human research protection training requirements.

HIPAA Education

At UP, researchers whose research is subject to Health Insurance Portability and Accountability Act (HIPAA) regulations must also complete the online "HIPAA Training Module" provided by PSU or participate in another qualifying HIPAA training program at their home institution.

At COM, education on HIPAA requirements is incorporated in the CITI course, in addition to the HIPAA training that all employees and students at COM are required to complete before beginning at the Medical Center.

Department of Defense (DOD) Supported Research Education

At UP, researchers whose research is supported by the DOD or conducted at DOD facilities or with DOD personnel must meet additional requirements depending on the DOD component involved. When a research study is submitted for review, if the study is supported by or conducted with the DOD, IRB staff

contact the principal investigator to go over the additional requirements applicable to the study. This training is conducted on a case-by-case basis.

For IRB members, an IRB education session at the full IRB meetings was dedicated to the DOD requirements. Also, when a full review study involves the DOD, IRB staff use the DOD guideline to ensure the additional requirements have been met. IRB staff were trained one of their weekly meetings on the DOD's additional requirements. As new IRB members and IRB staff are added refresher sessions will be provided.

At COM, researchers whose research is supported by the DOD or conducted at DOD facilities or with DOD personnel must meet additional requirements depending on the DOD component involved. When a research study is submitted for review, if the study is supported by or conducted with the DOD, IRB staff contact the principal investigator to go over the additional requirements applicable to the study. This training is conducted on a case-by-case basis.

IRB staff and members will be trained on the additional requirements for review of DOD research, and refresher training is provided when research involving Department of Defense requirements is presented for review. During the review of DOD research, IRB reviewers and staff use the DOD guideline to ensure the additional requirements have been met.

Educational Resources

In addition to the on-line, self-paced tutorials and recorded presentations, PSU provides the following means for on-going education to members of the research community:

- Seminars sponsored by the IRB, ORP and HSPO
- Educational presentations to departments and groups
- Educational internet site that provides access to information on human participant protection requirements, forms and instructions
- Individual and departmental consultations
- An electronic notification service to deliver regular informational updates on human participant protection requirements and offerings
- Research newsletters that include a variety of general interest information for researchers
- A lending library of books, videos, and CD ROMs on various topics related to human participant protection

B. IRB Members

Upon appointment to the IRB, new members undergo an IRB orientation and training process either individually or as a group to review IRB procedures and the general regulatory framework from which procedures and policies are derived. The materials and instruction for new members includes reviewing IRB member responsibilities, regulatory requirements and ethical criteria, institutional policies and other guidance documents. UP IRB members must the basic online training and online HIPAA training. COM IRB members must also complete the internet-based CITI Course in The Protection of Human Research Subjects.

Continuing education requirements for IRB members consists of participation in education and informational sessions presented at the beginning of convened IRB meetings. Relevant materials (periodicals, news or journal articles on human participant protection) are distributed for ongoing education. IRB members may attend IRB educational seminars conducted by the ORP or HSPO. In

addition, opportunities to attend relevant regional and national workshops and conferences are also offered to IRB chairs and IRB members when funds are available.

C. ORP and HSPO Staff

All staff receive a detailed job description outlining their responsibilities and the written procedures of the specific processes for which they are responsible.

Staff members are required to complete the IRB orientation and training for new IRB members. Staff members receive one-on-one training to learn their functions and participate in additional training on specific topics. Staff meetings are held to provide updates and discussion.

Staff members participate in the continuing education activities for IRB members and may attend the IRB educational seminars. Staff with regulatory responsibilities participate in on-line information and educational resources, such as the IRB Forum discussion group and notification lists.

The HSPO and ORP maintain subscriptions to semi-monthly periodicals on human participant protection, which are circulated to office staff, the IRB and others, as applicable.

Funds are appropriated for staff members when available to: (1) attend national and regional conferences and workshops on human participant protection; (2) gain membership in professional associations for human participant protection; and (3) pursue certification in human participant protection. Time is allotted during the work week for staff to participate in institutional employee meetings and training opportunities.

Staff participate in a performance evaluation process at least annually where they are provided opportunity to comment on their job performance and receive feedback from supervisors.

D. Participant Outreach

Educational presentations on human participant protection by the IRB leadership, HSPO/ORP staff are provided upon request to community groups or organizations. Educational internet content is posted to provide the community with information on the institution's human participant protection programs. The ORP/HSPO staff also represent the human participant research program and provides educational information at invited community sponsored fairs and events. At UP, IRB Coordinators are required to provide at least one community discussion per year such as talking with students at local high schools, support groups, etc.

The IRB office will track and review its involvement in outreach activities during the year, including the types of IRB presentations provided and involvement in community events and health fairs. A summary of presentations and participant outreach activities will be reviewed annually by Senior IRB Administration to assess the number and types of activities provided, the IRB staff involvement in these activities, and the types of groups reached through these activities, as well as to identify gaps and opportunities for future outreach.

The IRB web pages devoted to participant information will be reviewed quarterly by assigned personnel, or more frequently as needed, to verify links and update content. Institutional brochures for participant outreach will be reviewed at least annually by assigned personnel to ensure the content and contact information are current. Other IRB materials created for distribution to participants during events and

presentations will be reviewed and updated annually or prior to the next use, as needed by assigned personnel.

XX. AVAILABILITY OF COMPENSATION FOR AN INJURED RESEARCH PARTICIPANT

Unless specified by an outside funding agency, The Pennsylvania State University's policy is to not make compensation available to a participant who becomes injured during participation in a research study conducted at The Pennsylvania State University or by Penn State University employees. An injury clause is included in the informed consent document when any risk of injury exists (physical or psychological). Depending on the research being conducted, the following injury clauses are used:

- University Park: "In the unlikely event you become injured as a result of your participation in this study, medical care is available. It is the policy of this institution to provide neither financial compensation nor free medical treatment for research-related injury. By signing this document, you are not waiving any rights that you have against The Pennsylvania State University for injury resulting from negligence of the University or its investigators."

- College of Medicine: "It is possible that you could develop complications or injuries as a result of participating in this research study. It is the policy of HMC/PSU to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to your insurance carrier or to you. Some insurance companies may not cover costs associated with research studies. If for any reason these costs are not covered by your insurance, they will be your responsibility."

For sponsored research studies, the research agreement with the sponsor addresses medical care for research participants with a research-related injury. IRB staff review the agreement and the consent document for consistency regarding who is responsible to provide and pay for medical care for research-related injuries.

XXI. MECHANISMS TO ASSURE THE IRB IS FOLLOWING WRITTEN POLICIES AND PROCEDURES

Written policies and procedures are available to IRB members and ORP/HSPO office staff via paper or electronic form. Senior IRB Administration are charged with insuring that all approved policies and procedures are followed. If this is not the case, the Senior IRB Administration notifies the staff or IRB members of any deviation and proposes methods for correction or revision, if appropriate.

XXII. MECHANISMS FOR PERIODIC REVIEW OF POLICIES AND PROCEDURES

The IRB Standard Operating Procedure (SOP) manual is written and maintained by the ORP and HSPO and approved at COM by the IRB Executive Committee. This manual outlines the specific details of PSU's policies and procedures for following Federal, state, and local regulations for the ethical and safe conduct of research and the protection of human participants. Applicable sections are updated as

necessary to reflect changes in Federal, state, and local regulations and PSU's policies. The manual is reviewed at least every 36 months by Senior IRB Administration and is available on the ORP/HSPO website.

Institutional Review Board The Pennsylvania State University Penn State College of Medicine Penn State Milton S. Hershey Medical Center	PENNSTATE 1855
Standard Operating Procedures	**Policy Number:** **Version 11-18-2009**
Replaces: Ver. 4-18-2009	**Effective: May 24, 2010**
Authorized: Kevin Gleeson, M.D.	
Reviewed and Approved by: IRB Executive Committee	