



## **Guidance: Scientific and Scholarly Validity of Human Subject Research**

The scientific and scholarly validity review is conducted in the following manner:

For federally sponsored research, the peer review process (e.g., during the study section sessions) provides scientific and scholarly review.

For research subject to FDA review, there is a rigorous review that includes the scientific design of the research (e.g., during the IND or IDE evaluation stage).

For research conducted within the University of Pennsylvania's Cancer Center, the Clinical Trials Scientific Review and Monitoring Committee provides scientific and ethical evaluation.

For both department-funded research and that conducted by faculty without external sponsorship, the signature of the chair of the departments or the deans of schools have responsibility for ensuring that scientific review of the protocol has occurred.

For student research, the faculty sponsor named on the IRB application is responsible for ensuring the scientific and scholarly validity of the proposed research.

The IRB evaluates whether the design of the research protocol is sound and minimizes risks to participants. For protocols where the protocol design is unusual or novel, in addition to the protocol being assigned to primary reviewer(s) with relevant expertise, input from ad hoc consultants is also obtained.

The principal investigator should present information in the protocol to justify the statistical basis for the protocol design, the number of subjects per comparison group and the ability to identify and recruit such number of subjects during the proposed duration of the investigation.

If there is any question raised in the mind of the IRB reviewer that the research will not achieve the objectives proposed, the following steps should be considered. If the protocol is scheduled for independent scientific review by an internal or external peer review body, the IRB reviewer may condition enrollment in the research trial on the submission of written documentation of the approval by the internal or external peer review group. The IRB will not authorize an approved informed consent until such documentation is received and approved by the Executive Chair or other IRB member authorized by the IRB.

The IRB reviewer may contact the principal investigator to clarify the issue. If contacted, the principal investigator must be advised to provide follow-up with the submission of written material that summarizes the discussion with the IRB reviewer.

The IRB reviewer, wishing to remain anonymous, should contact the IRB Chair or Executive Chair with their concerns. The Chair may contact the investigator directly or through written correspondence generated by the IRB coordinator. The principal investigator must be advised to follow-up with the submission of written material that summarizes the discussion with the IRB Chair.

If it is unclear whether there will be external or internal review the IRB may request that the department chairperson conduct such a review employing either internal or external resources and provide a report to the IRB.

If the IRB reviewer, Chair or Executive Chair does not receive sufficient information to resolve the question they may request the HRP Director to obtain an independent consultant opinion.

The consultant will be chosen by the Executive Chair. The consultant may be internal or external depending on the advice of the Executive Chair. The result of the consultant's review will be submitted to the IRB. Such external consultants are not to be considered voting members of the IRB.

## **ANCILIARY REVIEW**

Penn has a number of entities that review human subjects' research protocols. These Ancillary Entities have jurisdiction over research protocols that involve certain procedures. For example, studies that involve MRI procedures for research purposes must be reviewed by the Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS). The IRB can grant approval of research protocols before they are reviewed by the ancillary entity but subjects are not permitted to be enrolled until review has occurred. This section details the processes in place to ensure that the IRB accounts for Ancillary Entity review during the review process.

## **EHRIS - RADIATION RESEARCH SAFETY COMMITTEE/RADIOACTIVE DRUG RESEARCH COMMITTEE**

The Penn Environmental Health and Radiation Safety Committee oversees both the Radiation Research Safety Committee (RRSC) and the Radioactive Drug Research Committee (RDRC). Both of these sub-committees review Human Research Protocols in conjunction with approval from the IRB.

- **RRSC-**

The Radiation Research Safety Committee (RRSC) reviews most research protocols involving ionizing radiation exposure to subjects solely as a result of participation in the research protocol. The RRSC also reviews research protocols for affiliated institutions, such as the Children's Hospital of Philadelphia, Pennsylvania Hospital and Penn Presbyterian Medical Center. RRSC review and approval is needed for human research protocols involving the administration of ionizing radiation to humans solely as a result of participation in a research study (with the exception of protocols that are reviewed by the RDRC). When making a determination about the necessity of RRSC approval of a protocol, it is useful to ask the following question: "Would the individual receive the radiation dose even if they were not enrolled in the research protocol?" If the answer is "yes", then RRSC review and approval is not required.

Only protocols that have been submitted via the HS ERA system (Penn) or eIRB system (CHOP) may be reviewed by the Committee. Notification of a protocol's need for review by the Committee and its availability are made when the PI indicates that radiation is used solely for research purposes on the HS ERA or eIRB online application.

For protocols requiring RRSC review, IRB Approval may be granted prior to RRSC review however, any requirements from RRSC review must be incorporated via modification prior to beginning subject enrollment.

- **RDRC-**

In certain situations, human research protocols involving the use of radiopharmaceuticals may be reviewed by the Radioactive Drug Research Committee (RDRC). However, the criteria for reviewing protocols under the RDRC is very specifically defined by the FDA regulations in 21 CFR 361.1.

To be eligible for review by the RDRC under 21 CFR 361.1, a protocol must:

- Involve certain radioactive compounds generally recognized as safe and effective;
- Be designed to use the radioactive compound to obtain basic information regarding the metabolism of the compound or regarding human physiology, pathophysiology, or biochemistry;
- Not be intended for immediate therapeutic or diagnostic use;
- Not propose to determine the safety and effectiveness of the drug (i.e., to carry out a clinical trial);
- Not be designed as part of the routine medical management of patients with a particular condition.

The RDRC also reviews research protocols for affiliated institutions, such as the Children's Hospital of Philadelphia, Pennsylvania Hospital and Penn Presbyterian Medical Center.

For protocols requiring RDRC review, IRB Approval may be granted prior to RDRC review however, any requirements from RDRC review must be incorporated via modification prior to beginning subject enrollment.

### **INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REVIEW PROCEDURES**

The IBC is responsible for providing review and oversight to ensure that all forms of research conducted at the University of Pennsylvania and within the University of Pennsylvania Health System are in compliance with the NIH Guidelines and all of the University's policies for use of the following:

- recombinant or synthetic DNA (r-s-DNA)
- infectious agents,
- human and non-human primate materials (including established cell lines),
- select agents,
- biosafety level 3 (BSL-3) research
- and human gene transfer

For protocols requiring IBC review, IRB Approval cannot be granted until IBC approval is granted.

Once notification of IBC approval is received, the submission can be placed for approval and a stamped consent form may be released, assuming all other IRB stipulations are met.

### **CENTER FOR MAGNETIC RESONANCE IMAGING & SPECTROSCOPY (CAMRIS)**

The overall mission of CAMRIS is to provide oversight in the responsible use and application of Magnetic Resonance Imaging in research. In order to ensure safety and to communicate proper risk/benefit information to subjects who may consent to MRI research within CAMRIS, they require that certain risk information be included in each consent form. The required clauses are broken up into two categories: those studies that are using experimental sequences and/or coils, and those that are using standard sequences and/or coils. CAMRIS also provides important safety information regarding the use of Gadolinium based contrast agents. CAMRIS conducts independent reviews of research protocols in order to provide guidance to research teams regarding MRI policy, procedures and subject safety. Research teams may be required to submit a CAMRIS application in addition to identifying use of MRI in the HSERA application.

Research that requires CAMRIS review may be approved by the IRB prior to receiving CAMRIS approval, however enrollment of subjects may not begin until CAMRIS approval is granted and CAMRIS approved risk language is inserted into the consent form. The standard language for MRI scans is publicly available on the CAMRIS website.

## **CENTER FOR ADVANCED COMPUTED TOMOGRAPHY IMAGING SERVICES (CACTIS)**

The purpose of the Center for Advanced Computed Tomography Imaging Services (CACTIS) is to facilitate productive research within the guidelines set forth by the Institutional Review Board (IRB) of the University of Pennsylvania for human study subjects. Under the direction of the Chair, Dr. Harold Litt, the CACTIS committee reviews proposed research requests and makes decisions and recommendations accordingly. CACTIS will review proposed research protocols involving humans, animals, phantoms or specimens prior to initiation of the project. This review process has two major goals:

- To ensure all research performed within the CT facilities complies with CACTIS policy, University policy, and Federal Regulations
- To analyze proposed research requirements for safety and feasibility, and to identify the resources needed to carry out each research protocol (including personnel, software, hardware and scan time)

CACTIS also determines whether the CT risk information in the informed consent form is appropriate for the proposed research. Research that requires CACTIS review may be approved by the IRB prior to receiving CACTIS approval, however enrollment of subjects may not begin until CACTIS approved risk language is inserted into the consent form. The standard language for CT scans is publicly available on the CACTIS website.

## **CLINICAL TRIALS SCIENTIFIC REVIEW AND MONITORING COMMITTEE (CTSRMC) REVIEW PROCEDURES**

The Cancer Center's Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) are tasked with reviewing and tracking all cancer related research, with few exceptions. IRB approval of cancer related research protocols can occur prior to CTSRMC review, but subjects are not permitted to be enrolled until CTSRMC review has occurred or been determined to be not applicable. It is also recommended that CTSRMC review take place prior to IRB review, for investigator initiated protocols, to prevent significant scientific questions from affecting the ethical review.

If CTSRMC review occurs before IRB review, the IRB may be forwarded a copy of the CTSRMC decision letter for review of any stipulations that may impact the IRB's approval criteria. Prior to the convened meeting the IRB Administrator will contact the study team to request for a response to any stipulation that could impact the IRB's approval criteria and upload the CTSRMC decision letter to the HSERA application in order to allow IRB Members access to this letter. The IRB Administrator will share any responses from the study team with the IRB Members to be considered during the convened meeting. If a stipulation impacts the IRB's approval criteria and is not addressed prior to IRB review, the IRB decision letter will include a stipulation similar to the CTSRMC's stipulation.

Once notification of CTSRMC approval is received, the submission can be placed for approval and a stamped consent form may be released, assuming all other IRB stipulations are met.

## **HUMAN RESEARCH ADVISORY COMMITTEE (HRAC) REVIEW PROCEDURES**

The mission of the Human Research Advisory Committee (HRAC) is to advise the Vice Provost for Research on the potential institutional impact of issues related individual research protocols (specifically use of gene transfer), and research programs when appropriate. HRAC may also advise on issues related to overall institutional approach to the execution of human research and interests of the institution that could potentially impact the conduct of any specific human subjects' research protocol or the integrity of the Human Research Protections Program (HRPP)

The IRB Associate Director will act as a liaison between the IRB and the HRAC to determine if formal review is required. Once the determination is made, the Director informs the IRB Administrator. Either the Director or the IRB Administrator will contact the study team to inform them of the requirement for HRAC review.

Once notification of HRAC approval is received, the submission can be placed for approval and a stamped consent form may be released assuming all other IRB stipulations are met.

## **HUMAN STEM CELL RESEARCH ADVISORY COMMITTEE (HSRAC) REVIEW PROCEDURES**

The Human Stem Cell Research Advisory Committee (HSRAC) is charged with review of certain research protocols that involve human embryonic and human induced pluripotent stem cells. This section details the processes in place to ensure that the IRB accounts for HSRAC review during the review process.

The IRB Staff, as part of the completeness check process for initial submissions, modifications or requests for continuing review, may identify through the screening of the HSERA application that HSRAC review is required. If the study is determined to meet the definition of human subjects' research, IRB approval cannot be granted until HSRAC committee review and approval has been granted or the HSRAC Administrator has confirmed that HSRAC review is not required.

Once notification of HSRAC approval is received, the submission can be placed for approval and a stamped consent form may be released assuming all other IRB stipulations are met.

Often, stem cell research protocols submitted to the IRB will not meet the definition of human subjects' research. Regardless of the level of IRB review required for the protocol, the IRB Associate Director should be engaged and HSRAC should be notified of any study involving human embryonic and/ or human induced pluripotent stem cells. Final determinations for IRB review should be on hold until HSRAC has either confirmed that their formal review is not required, or provided a formal review determination about the research.

## **CHPS/CTRC Resources**

The Center for Human Phenomic Science (CHPS) [formerly the CTRC-Clinical and Translational Research Center] provides resources, environment, operations, and training to support and promote high-quality clinical and translational research by qualified investigators.

Within CHPS, the Study Design and Biostatistics (SDAB) Core works closely with existing resources to provide targeted study design and biostatistics support to ITMAT/CTSA investigators. The Core serves as a direct provider of services, including protocol review, study design, proposal development, and performance of simple to potentially substantial complex analyses. SDAB integrates the support available with the HUP and CHOP Center for Human Phenomic Science (CHPSs), the expertise and resources of faculty in the Center for Clinical Epidemiology and Biostatistics / Department of Biostatistics and Epidemiology (CCEB/DBE), and the Biostatistics Analysis Center (BAC).

CHPS provides resources for design, setup, conduct and close-out/ publication phases of clinical research. CHPS offers a facilitator service at no charge to help design and implement clinical research studies within the CHPS at the time of grant application to enhance the research design and to communicate details regarding CHPS resources and costs. For funded applications, a CHPS facilitator can meet with investigators and their coordinators to help obtain CHPS and

IRB protocol approval. After approval, a CHPS facilitator will continue to work with the study team to initiate the protocol.

CHPS also provides resources for investigational product accountability and destruction, database quality control and finalization, subject un-blinding and follow up as well as coordination with the IRB and other Penn Ancillary review entities throughout the duration of the research.

Investigators must apply for CHPS support through HSERA by filling out a CTRC request. IRB approval of research may be granted prior to approval from CHPS, however any changes requested by CHPS must be incorporated via HSERA modification or initial response prior to beginning enrollment.