HUMAN SUBJECTS

The Johns Hopkins University is deeply committed to the protection of human research subjects. The mission of the Human Research Protection Program (HRPP) of Johns Hopkins Medicine is to ensure that research at Johns Hopkins meets the highest possible scientific, ethical, and regulatory standards. This mission is accomplished through a) high quality education and training in the ethical conduct of research, b) a robust ethics review infrastructure and c) rigorous oversight that ensures compliant research. **For ICTR studies, all JH ICTR partner Institutions will operate according to the standards for the protection of human subjects established by the Johns Hopkins University.**

Any protocol funded by this application involving human subjects will require IRB approval and be subjected to the full oversight of the Johns Hopkins HRPP.

A. Education and Training:

Johns Hopkins is committed to ensuring those engaged in human subjects are well-educated about the applicable regulatory and ethical requirements and have the educational tools necessary to conduct compliant research. Its educational programming includes both required and optional courses as detailed below.

A.1: Core Required Training:

All persons engaged in human subjects research at Johns Hopkins are required to complete a comprehensive curriculum in human subjects protections courses before conducting human subjects research. The required "IRB Compliance Training" is comprised of three core courses. The course descriptors, including a summary of required course modules is as follows:

Basic Human Subjects Research

This course provides a broad overview of the ethical background for regulations in human subjects research, as well as an overview of the IRB review requirements to be met before a human subjects research project may begin. The modules included in this curriculum include:

- History and Ethics of Human Subjects Research
- Defining Research with Human Subjects - SBE
- Basic Institutional Review Board (IRB) Regulations and Review Process
- Informed Consent
- Privacy and Confidentiality - SBE
- Social and Behavioral Research (SBR) for Biomedical Researchers
- Records-Based Research
- Genetic Research in Human Populations
- Populations in Research Requiring Additional Considerations and/or Protections

Conflict of Interest and Commitment

This course is designed to introduce researchers to the topic of financial conflicts of interest in research, including what financial conflict of interest means, sources and risks of financial conflicts of interest in research, federal regulations and institutional policies designed to address the risks, and researchers' obligations under federal and institutional regulations and policies. This course is designed to fulfill the training requirements included in the federal regulation and in Johns Hopkins policy.

After completing this course, researchers will be able to:

- Define key terms, including investigator, conflict of interest (COI), related research, and financial conflict of interest (FCOI).
- Describe both federal regulations and institutional policies regarding FCOIs in research.
- Describe the requirements that apply to investigators.
- Describe the requirements that apply to the Institution.
- Identify noncompliance with disclosure requirements and/or management of FCOIs.
- Apply learned information while reviewing a hypothetical FCOI.

HIPAA For Research

This course assumes the researcher has a basic understanding of the HIPAA requirements. JH workforce members who are required to complete this course must first complete the required, applicable basic privacy course. At the end of this course, researchers should be able to:

- Explain how HIPAA affects the use and disclosure of health information in research
- Describe the scope of their responsibility for protecting the privacy and security of research data
- Recognize how to de-identify health information for research
- Explain how limited data sets may be used and disclosed for research

In addition to the IRB Compliance Training required for all study team members new PIs and fellows must complete additional training through the REWards program.

The **Research Ethics Workshops About Responsibilities and Duties of Scientists (REWards)** program, designed in conjunction with faculty from the Berman Institute of Bioethics combines lectures and small group discussions to provide practical information on the ethical issues involved in research protocol development and implementation. Following this program, the participant must demonstrate that they can 1) describe the context for the development of research ethics at the national and local levels, 2) recognize aspects of study design that can be ethically problematic, including subject selection, research-related risks, conflicts of interest, and use of vulnerable populations, 3) describe the key concepts in informed consent, including respect for autonomy, voluntariness, decision-making capacity, disclosure of information, and understanding, 4) describe methods of protecting privacy and confidentiality in the context of human subjects research and 5) recognize the key concepts in the responsible conduct of research, including data acquisition and management, mentor/trainee responsibilities, publication practices and authorship standards, conflicts of interest and commitment, and scientific misconduct. New Principal Investigators must complete their requirement to attend REWards within one year from the date of their first eIRB protocol submission as a PI. PIs must attend 2 workshops to fulfill their training requirement. If the PI does not complete REWards within 1 year from the date of their first eIRB submission, they will not be able to submit new applications or changes in research until the requirement has been met. Fellows must complete their requirement to attend REWards by the end of their fellowship and must also attend 2 workshops to fulfill the training requirements.

A.2: Recertification

In February 2011, the Johns Hopkins Medicine Human Research Protection Program implemented new compliance training recertification requirements for principal investigators engaged in human subjects research. Analogous to continuing education in clinical practice, compliance training recertification in human subjects research is designed to help investigators reflect on how research ethics principles and standards apply to their research, learn about new regulations and strategies for protecting the rights and welfare of human research subjects, and demonstrate their commitment to ongoing quality improvement in their research. Principal Investigators are required to complete HSR training recertification every 3 years**.** The following are the significant components of the compliance training recertification requirements. Recertification includes 4 required online modules and 1 in-person activity.

The four mandatory courses/modules include:

- Responsible Conduct of Research
- Refresher Course GCP: Informed Consent–An Ongoing Process
- Refresher Course: An Over view of Research with Vulnerable Subjects
- Refresher Course GCP: Conducting Investigator-Initiated Studies According to FDA Regulations and Good Clinical Practices

The list of in-person activities includes a variety of instructor-led courses and in-person workshops offered throughout the calendar year. In-person, instructor-led continuing education is primarily offered through a the REWards course or the ICTR sponsored workshops on Bringing the Science of Safety to Research, Conducting Research in the Community, and The Role of Data and Safety Monitoring Boards. Limited other learning activities at the institutional, departmental or divisional levels – such as Grand Rounds, lectures, conferences or seminars may also qualify towards the in-person recertification requirement provided the

content focuses on research ethics and the activity is approved by the Human Research Protection Program.

In January 2015, the Johns Hopkins Medicine Human Subjects Protection Program extended the recertification requirements to study team members (non-Principal Investigators) engaged in human subjects research. Similar to the recertification requirements for PIs, study team members must meet the recertification requirements every three years. Recertification includes the same four required online modules as required for PIs and two additional elective online modules. All online modules are available through CITI (Collaborative Institutional Training Initiative) with registration for the courses via myLearning, JHU's online learning platform.

Study team members may choose **two** additional online modules from the options below:

- Refresher Course: Genetics Research
- Refresher Course: Pregnant Woman and Fetuses
- Refresher Course: FDA Regulated Research and Conference on Harmonization
- Refresher Course: Records Based Research Refresher Course: Social and Behavioral Research
- Refresher Course GCP: Overview of New Drug Development
- Refresher Course GCP: International Conference on Harmonization (ICH): GCP Requirements
- Refresher Course GCP: International Conference on Harmonization – ICH for Investigators
- Refresher Course GCP: Investigator Obligations in FDA-Regulated Clinical Research
- Refresher Course GCP: Managing Investigational Agents According to GCP Requirements
- Refresher Course GCP: Conducting Clinical Trials of Medical Devices
- Refresher Course GCP: Detection and Evaluation of Adverse Events
- Refresher Course GCP: Reporting Serious Adverse Events
- Refresher Course GCP: Monitoring of Clinical Trials by Industry Sponsors

If a study team member later becomes a principal investigator, then they must take the principal investigator recertification at the next three year renewal period.

A.3: Additional Required Training:

In addition to the core training requirements noted above, individuals engaged in human subjects research must complete the following additional training, as applicable.

Responsible Conduct of Research (RCR) Program:
The RCR Program is designed to educate all faculty, postdoctoral trainees, and staff engaged in research at JHU on topics related to research integrity. Applicable researchers must complete each component of the RCR program every four years. The RCR Program includes the following required components:

1. Completion of the online RCR course developed by the Collaborative Institutional Training Initiative (CITI), comprised of seven modules. Completion of all modules is required.
2. The Research Integrity Colloquia: In this series, JHU faculty discuss their perspectives on approaching and conducting research with integrity. Interactive presentations covering a broad spectrum of RCR topics are held over the course of the academic year.
3. Attendance at one Department/Division Meeting where an RCR topic is discussed.

Good Clinical Practice (GCP) Training
Principal Investigators and study team members subject to the NIH requirements for GCP training must either complete the online GCP course available through CITI or complete an alternate GCP course approved by TransCelerate. Recertification is required every three years.

Clinical Research Billing Orientation (CRBO) and Clinical Research Management Systems (CRMS):
If there will be billing for study procedures, CRBO is required for PIs, and for study team members who will consent participants. This online course introduces study team members to the improved clinical research billing process. Live training sessions, reference materials and start-up support supplement this overview. For studies that require CRBO training, study teams are also required to track study enrollment in the CRMS. CRMS training must be taken by the PI and the study team members responsible for entering data in the CRMS.

A.4 Optional Training

Johns Hopkins offers a diverse curriculum of optional trainings to enable researchers to remain knowledgeable in the changing research landscape. Training is offered through several JH programs to afford flexibility in scheduling. Select optional training includes:

A.4.1 Training offered by the Office of Human Subjects Research

eIRB 101: Prepare and Submit an Application: This 2 hour in-person course is an introduction to the Johns Hopkins School of Medicine's Electronic Institutional Review Board (eIRB) System. The course is aimed to help researchers gain a better understanding of how to prepare and submit an IRB application, how to respond to IRB issues, how long the review process takes, and how to submit post-approval amendments, annual reviews, adverse events and terminations.

The **New Investigator Boot Camp** is a 4-hour intensive course available to new investigators two times per year. The course orients investigators and study-team members to the basic workings of the JHM IRB to familiarize researchers with the steps to prepare and submit an IRB application to conduct Human Subjects Research at Johns Hopkins University School of Medicine and School of Nursing.

IRB Open House: An annual event, open to the entire research community that is designed to connect IRB personnel and personnel from other research support offices to study team members. Thirty minute sessions on select topics of interest are featured. Topics include items such as a) consent form tips & tricks, GCP/monitoring, single IRB review, common application errors and IRB operational workflows.

The **Compliance Monitoring Program Educational Series** is a live seminar offered biannually to the Johns Hopkins University investigator community. This one-hour seminar covers new or updated policies that concern Human Subjects Research conduct and compliance with applicable institutional and Federal requirements, while also presenting best-practices strategies to maximize compliance.

The **GCP and Investigator Responsibilities Lecture** is conducted approximately every 2 years for the JH Hospital affiliated of Suburban, Sibley Memorial, and Howard County General hospitals. The course is available for faculty interested in undertaking human subjects research. The course is also available upon request.

Targeted trainings: Staff of the Office of Human Subjects Research regularly present on IRB expectations and review processes at annual events such as JH Nursing Scholar's Days and as invited speakers for research groups and undergraduate and graduate level classes.

A.4.2 Training supported by or involving faculty of the Institute for Clinical & Translational Research (ICTR)

Graduate Training Program in Clinical Investigation (GTPCI)/Science of Clinical Investigation (SOCI) is a Ph.D. and certificate awarding program offered through the JHSPH. It covers the fundamentals of clinical research: regulatory, research ethics, biostatistics, clinical trial design, etc. This training program features a session focusing on Good Clinical Practice (GCP) and Standard Operating Procedures (SOPs). This seminar is part of the Research Ethics course, and is offered annually in the Fall academic semester as an in-person course and online. Program reference materials and references are available through the ICTR.

The Research Coordinator Training Program (RCTP) is a three day intensive course offered through the JH School of Nursing 2-3 time per year. Upon completion, attendees are awarded a certificate of completion. The program covers research ethics, informed consent, budget, QA/QC, site organization, etc. ICTR-supported staff teach two sections: QA/QC and Regulatory File Maintenance. The program is endorsed by the ICTR and is required for the ICTR's Study Coordinator and Mentorship Program (SCAMP) students. As an alternative to the three-day in-person course, online modules are available for new research staff.

The **Research Coordinator First Friday Webinar Series** is an online series offering ongoing education in topics relevant to ethical and compliant research conduct. Topics include: a) Responsibilities of an IND sponsor, ethical factors in the recruitment and retention of research participants, ICH GCP E6 requirements, preparing for and surviving an FDA inspection, clinicaltrials.gov requirements, use of EPIC and CRMS and tips for preparing for monitoring visits.

The **Research Participant Advocates** offer training tailored to specific research to study teams in private seminars. Trainings offered are Informed Consent, Good Clinical Practice, Adverse Event Recognition and Reporting, Standard Operating Procedure development and Data Safety and Monitoring.

The **ICTR Research Coordinator Clinical Training program** offers clinical skills training for unlicensed study team members aimed at ensuring that study team members are properly trained in clinical tasks they may be asked to perform as part of the study.

The Berman Institute of Bioethics offers a **Seminar Series** and **Ethics for Lunch** series featuring case-discussions and lectures highlighting a variety of ethical issues.

B. Ethics and Regulatory Review

The Human Research Protection Program (HRPP) of Johns Hopkins Medicine provides a robust ethics and regulatory review infrastructure that supports the ethical and compliant conduct of research. The HRPP of JHM initially received full accreditation from AAHRPP (the Association for Accreditation of Human Research Protection Programs) in 2005. Since then it has been reaccredited in 2008, 2011 and 2016.

The Office of Human Subjects Research (OHSR) within the School of Medicine is comprised of 38 staff members that support JHM's 7 IRBs. The staff includes a team of dedicated consent form specialists, a compliance team comprised of four licensed attorneys, and three full-time compliance monitors. Each IRB Committee meets weekly with the exception of the IRB located at Johns Hopkins All Children's Hospital which meets monthly. Each committee includes both the required community representative and a faculty member with formal research ethics training. Six of the 7 committees also include a dedicated pharmacy representative. The exception is IRB X which does not review studies involving drugs.

In addition to the IRBs, JH has a robust system of ancillary review committees to ensure research is compliant with all applicable regulatory requirements. As examples, these include the Conflict of Interest Committee, Clinical Radiation Research Committee, Images and Recordings Oversight Committee, Data Trust Research Sub Council, Maternal Fetal Medicine Committee, and the Sidney Kimmel Comprehensive Cancer Center Clinical Research Office.

Of the ancillary review committees, the High Risk Review Committee (HRRC) is of particular import. The HRRC is divided into two groups, one at Johns Hopkins Hospital (JHH) and a second at Johns Hopkins Bayview Medical Center (JHBMC). These committees are comprised of highly experienced researchers and research support staff within the location for which they perform reviews. Members are appointed by the Vice Dean for Clinical Investigation. HRRC members have access to (i) the credentials and qualifications of local investigators and staff, and knowledge of (ii) the adequacy of the facilities for the safe conduct of the research. The role of each HRRC is to provide local site specific review and enhance human subject safety in high risk research conducted at JHH or JHBMC. Since 2014 over 300 protocols have been reviewed by the HRRC.

To ensure a robust ethics and regulatory review infrastructure, OHSR staff are fully integrated into other aspects of the JH research review process. Representatives from the OHSR also sit on several of these ancillary review committees, including the Conflict of Interest Committee, Data Trust Research SubCouncil, Images and Recordings Oversight Committee and the MyChart recruitment team.

OHSR compliance team members also participate in local research review committee (RRC) meetings. To ensure research conducted at any Johns Hopkins location is conducted in accordance with the same high ethical standards, RRCs have been established at each of the local hospitals/practices to allow for local input into the

research proposed in these settings. RRCs meet monthly at Howard County General Hospital, Suburban Hospital, Sibley Hospital and Johns Hopkins Community Physicians practice group.

To further ensure consistency in application of ethical and regulatory standards, Johns Hopkins has developed a regulatory team, comprised of IRB directors and compliance team members from each of JH's three IRB offices and legal counsel for both the University and Health System. This team meets bi-weekly to harmonize approaches and review regulatory changes that may impact human subjects protections.

Johns Hopkins appreciates that a robust ethical and regulatory review system must incorporate opportunities for consultation in the development of research protocols in the early stages, prior to IRB review. To this end the ICTR offers a research studio program, designed to provide high level consults to investigators. Components of the studio may include consultation on ethical or regulatory aspects of study design and guidance for development of robust data safety monitoring plans.

Additionally, since 2008 the ICTR has supported a research ethics consult service, led by Holly Taylor. The RECS has provided almost 150 consults over a wide range of topics to individuals as well as study teams from the Schools of Medicine, Nursing and Public Health. Often, these consults will include members of the specific communities targeted for the research.

Finally, a critical aspect of Johns Hopkins HRPP is its commitment to actively engaging community members to inform the ethics and regulatory review process. Through its Community Engagement program, the ICTR continues to educate the local community on the importance of clinical research, and the rights of the research subject when participating in a study and obtain feedback about ways in which research may be improved at Johns Hopkins. Annually, community members are invited to participate in a "Community Day at the IRB", observing an IRB meeting and having an opportunity to ask questions about the research review process and provide insights into mechanisms to enhance this process.

C. Compliance Oversight

Johns Hopkins is deeply committed to reinforcing the importance of adhering to regulatory and ethical requirements for human subjects protections through robust compliance monitoring and oversight programs.

The Office of Human Subjects Research Monitoring Program began in 2004. The primary function of the program has been to examine IRB approved protocols from two approaches: first, is the Routine Monitoring Visit; second, is the Directed Audit. A routine monitoring visit involves a planned examination of a JHM IRB approved protocol to assess and assure overall compliance with regulatory requirements and terms of IRB approval. Although all IRB approved research is eligible for a routine monitoring visit, priority is given to the following types of research activities:

- Research for which a Hopkins' study team member holds the IND or IDE number. In these cases, the FDA considers the Hopkins' faculty member to be the sponsor/investigator and he/she must fulfill all of the associated FDA regulations. All projects for which a Hopkins study team member is the sponsor/investigator must have a monitoring visit before the IND or IDE is used in the project.
- Research that involves recombinant DNA, infectious agents and/or pathogens, biological toxins, or gene transfer or pathogens introduced into human participants.
- Research projects that are more than five years old and for which there is a recent change in the principal investigator.

An IRB may also determine a protocol should be considered a priority protocol for monitoring. Directed audits may be requested either by a JHM IRB or by the Vice Dean for Clinical Investigation. The IRB may require an audit in cases where the IRB believes non-compliance with conduct of human subjects research has occurred. A directed audit may also be required in association with an investigation of a problem reported to JHU.

One of the most important aspects of JH's Compliance Monitoring Program is its emphasis on education. Johns Hopkins utilizes its compliance oversight activities as a mechanism to educate research teams about best practices and improve overall research compliance. Comprehensive tools are available through the compliance monitoring program that research teams may use to promote regulatory compliance in the conduct of the research. The Compliance Monitors also conduct a seminar twice each year to cover topics that arise during compliance visits and further explain the program goals. In-services are also provided upon request and may also be recommended by the JHM IRB.

Through the ICTR, an annual education program is offered for investigators on how to best constitute and use a Data and Safety Monitoring Board (DSMB). The ICTR also offers consultative help to any investigator looking for assistance with DSMB formulation and development of related materials, such as a DSMB charter.

To extend its educational support services to JH affiliates with whom Johns Hopkins researchers conduct research, the Johns Hopkins Clinical Research Network (JHCRN) has formed a QA program designed to establish monitoring standards and best practices for Network sites to ensure consistently compliant performance. The OHSR compliance monitoring program manager consults with Network coordinators to oversee monitoring efforts for the Network.

Johns Hopkins is committed to ensuring that the research subject experience is assessed as part of its compliance and monitoring efforts.

Through regular consent observations, experts in informed consent who are designated Research Participant Advocates (RPAs) observe study teams during the consent process with their research volunteers. Extensive feedback, individualized training and follow up is provided to assure we are optimizing the consent process at the institution. Researchers can volunteer to have the process observed, the RPA can initiate the process for studies that may benefit from the process or the IRB may initiate an observation if there are issues identified by an IRB review, a problem event report or a participant/study team complaint.

Research participant satisfaction is assessed through a semiannual survey of a random sample of research participants in the active phase of a protocol. Understanding of and satisfaction with the informed consent process as well as perception of the safety of the research experience are assessed. Results are posted on the ICTR website (http://ictr.johnshopkins.edu/news_announce/research-participant-satisfaction-survey-results/).