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PennState College of Medicine

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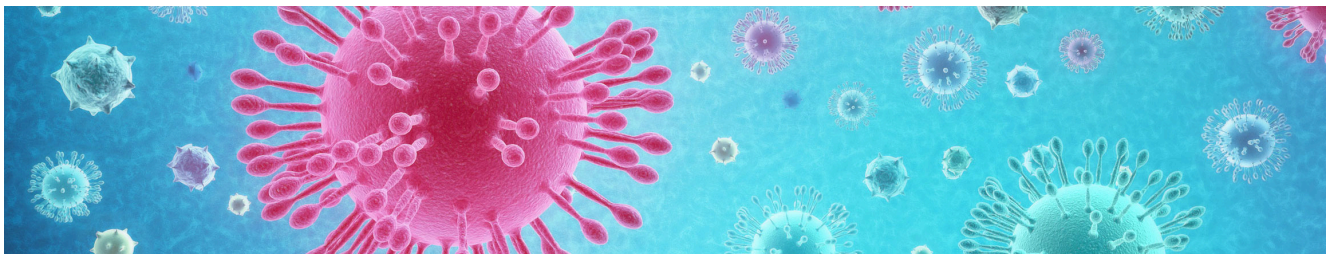
Clinical Research Guidebook



(https://med.psu.edu/coronavirus)

See all COVID-19 research updates, including updated human-subjects research guidance and participant screening script, here. (https://research.med.psu.edu/coronavirus)

This clinical research guidebook has been developed for faculty and staff members engaged in clinical research at Penn State College of Medicine/Penn State Health Milton S. Hershey Medical Center. It has been adapted from the materials created and released by The Clinical Trials Resource Group at the University of California – Davis CTSC.

Researchers at University Park may wish to view University Park-specific guidebook information (http://ssri.psu.edu/clinicalresearchguidebook).

REQUEST CLINICAL RESEARCH PROJECT HELP HERE (/REQUEST)

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SEARCH

Resources and Training

Overview

Penn State Health and Penn State College of Medicine conduct a variety of clinical research studies in accordance with the applicable regulations relevant to the protection of human subjects. For FDA-regulated research, Penn State commits to apply the “International Conference on Harmonisation – Good Clinical Practice as adopted by the U.S. FDA and as required by sponsors. Standardized training and continuing skill development of all clinical research professionals is an important part of preparation for clinical research. It is the responsibility of all staff and investigators to know, understand and maintain sufficient knowledge of the federal, state and local requirements protecting research subjects.

Laws Governing Clinical Research: Department of Health and Human Services

The U.S. Department of Health and Human Services (HHS) is the government’s principal agency for protecting the health of all Americans. It comprises several public health services agencies including the FDA (Food and Drug Administration), OHRP (Office of Human Research Protection), the NIH (National Institutes of Health), and the Centers for Medicare and Medicaid Services (CMS).

Regulatory Organization	Key Regulations
Health and Human Services (HHS)	• Code of Federal Regulation (CFR) 45 CFR Part 46 (Common Rule) • Federalwide Assurance
Food and Drug Administration (FDA)	• 21 CFR 312 (IND) • 21 CFR 812 (IDE) • 21 CFR 56 (IRBs) • 21 CFR 50 (Protection of Human Subjects) • 21 CFR 54 (Financial Disclosures) • 21 CFR 58 (GLP)
Centers for Medicare and Medicaid Services (CMS)	• National Coverage Decision • Local Coverage Decisions

Food and Drug Administration (FDA, fda.gov (https://www.fda.gov)) is responsible for protecting and promoting public health through the regulations and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), veterinary products, and cosmetics. Understanding these rules is critical for any investigator who conducts human subject studies with drugs, devices or dietary supplements, whether already approved on the market, or still investigational.

Office of Human Research Protection (OHRP, hhs.gov/ohrp (https://www.hhs.gov/ohrp)) provides leadership, guidance, and education in the protection of the rights, welfare, and well-being of subjects involved in research conducted or supported by the HHS. OHRP performs these services through providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research. Detailed regulations for human subject protection are listed on the OHRP website (https://www.hhs.gov/ohrp/regulations-and-policy/index.html). OHRP rules guide the Institutional Review Boards (IRBs).

National Institutes of Health (NIH, nih.gov (https://www.nih.gov)) seeks to provide fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability. As part of this mission NIH provides leadership and direction to programs designed to improve health and provides support for research.

The NIH funds over 60 Clinical and Translational Science Centers across the country. Working together as a national consortium, Clinical Translational Science Award (CTSA) institutions share a common vision to improve human health by transforming the research and training environment to enhance the efficiency and quality of clinical and translational research. The CTSA program is supported by the National Center for Advancing Translational Science (NCATS), part of the National Institutes of Health.

The CTSA program has the following overriding objectives:

- Provide a comprehensive array of essential tools and services to spark clinical and translational research.
- Ensure the training of a well prepared workforce of trainees, staff, and investigators.
- Effectively communicate the many tools, services, and training opportunities to ensure innovative translational science advances that will improve human health.

Today, Penn State Clinical and Translational Science Institute (ctsi.psu.edu (https://ctsi.psu.edu)) offers resources that faculty, trainees and staff across the scientific and medical spectrum can use to enhance research and improve health and healthcare delivery.

Centers for Medicare and Medicaid Services (CMS, cms.gov (https://www.cms.gov)) is the federal agency which administers Medicare, Medicaid, and the Children's Health Insurance Program. On June 7, 2000, the President of the United States issued an executive memorandum directing the Secretary of Health and Human Services to "explicitly authorize [Medicare] payment for routine patient care costs… and costs due to medical complications associated with participating in clinical trials." CMS responded to the executive order with the clinical trial policy – National Coverage Determination (NCD). Medicare State fiscal intermediaries also issue Local Coverage Determinations (LCD). Our intermediary is Novitas Solutions, Inc.

Understanding Coverage Rules is critical for generating correct billing claims for clinical research participants. At Penn State Health/Penn State College of Medicine, the tool and the process of applying CMS rules to each individual study is called **Coverage Analysis**. This information is reviewed in detail in the Preparing Documents (/research-support/guidebook/#topic-preparingdocuments) section of this guidebook.

Laws Governing Clinical Research: Code of Federal Regulations

The **Code of Federal Regulations (CFR)** is a compendium of the general and permanent rules and regulations published in the Federal Register by the federal executive departments and agencies. The CFR is divided into 50 titles that represent broad areas subject to Federal regulations. Title 45 CFR encompasses regulation of Public Welfare. Title 21 CFR is administered by the FDA and covers regulations of Food and Drugs.

Title 45 CFR 46 (The Common Rule (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html)) is a core set of regulations defining protection of Human Subjects in clinical research. 45 CFR part 46 includes four subparts:

- Subpart A (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html#subparta), also known as the Federal Policy or the "Common Rule"
- Subpart B (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-b/index.html), additional protections for pregnant women, human fetuses and neonates
- Subpart C (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-c/index.html), additional protections for prisoners
- Subpart D (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-d/index.html), additional protections for children

Through a system of IRB registration (https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/irb-registration/index.html) and assurances (https://www.hhs.gov/ohrp/federalwide-assurances-fwas.html), the Department of Health & Human Services (DHHS) regulations require institutions to commit to compliance with 45 CFR 46 before initiating participation in DHHS-conducted or -supported research involving human subjects. A Federalwide Assurance (FWA) is the institution's commitment to apply 45 CFR 46 as required. Penn State College of Medicine's FWA is **00004251**. In the FWA, Penn State Health is listed as a component of Penn State College of Medicine.

Title 21 CFR: The FDA regulations (Title 21 CFRs) are applicable when research is being conducted to develop a medical product that will be licensed for sale in the United States. Certain federally sponsored and privately sponsored research is subject to the regulations of the FDA according to 21 CFR Parts 50 and 56. Title 21 CFR part 50 defines regulations for informed consent and 21 CFR part 56 defines regulations for IRBs. These regulations largely overlap but are not identical with the Common Rule. Investigators need to know both sets of regulations to apply them appropriately.

Title 21 CFR 312 details the regulations for human research done with investigational drugs. This Title includes, but is not limited to, the regulations for applying to FDA to conduct research under an Investigational New Drug (IND) application (21 CFR 312 Subpart B), responsibilities of Sponsors and Investigators under an IND (21 CFR 312 Subpart D), and expanded access to Investigational Drugs (21 CFR 312 Subpart I). The IND and IDE Submissions section of this guidebook discusses the drug development process in more detail.

Title 21 CFR 812 details the regulations for human research with investigational devices. The regulations lay out the framework for applying to FDA to conduct human subjects research with Investigational Devices (21 CFR 812 Subpart B), responsibilities of Sponsors (21 CFR 812 Subpart C) and Investigators (21 CFR 812 Subpart E), and IRB approval 21 CFR 812 Subpart D).

The IND and IDE Submissions section of this guidebook discusses the drug development process in more detail.

Penn State Health Clinical Research Guidebook

This guidebook is updated on an annual basis at minimum to provide updates and new information. Always reference this website, not printouts, for the most recent information.

Investigator Manual

HRP-103 – Investigator Manual is designed to guide investigators and study team members through policies and procedures related to the conduct of Human Research that are specific to this institution. General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training.

It is recommended that all study team members review the Investigator Manual and become familiar with its contents. The manual is updated regularly and can serve as an initial source of information when questions arise regarding policies and procedures.

The manual can be located from the link below or accessed through the CATS IRB library.

ACCESS THE INVESTIGATOR MANUAL (HTTPS://WWW.RESEARCH.PSU.EDU/IRB/INVESTIGATOR-MANUAL)

Clinical Research SOPs and Competencies

Penn State College of Medicine Clinical Trials Office (CTO) creates and maintains multiple Standard Operating Procedures (SOPs) and competencies related to conduct of clinical research at Penn State College of Medicine and Penn State Health.

The SOPs as well as links to other institutional research resources can be found, including coordinator competencies, can be found on the Penn State Health Policy Portal (https://pennstatehealth.ellucid.com/) (ePass login required).

CITI Training

Penn State employs the Collaborative Institutional Training Initiative (CITI) program, a web-based training program to satisfy the training requirements for all personnel conducting human subject research as part of the University and/or Penn State Health.

For details on required modules, see IRB training and resources (https://www.research.psu.edu/IRB/Training) on the University Office of Research Protections website.

ACRP Enhanced Investigator Training

Penn State College of Medicine and Penn State Health have partnered with the Association of Clinical Research Professionals (ACRP) to support professional growth and development through providing membership accounts to users registered through the organizational account. User seats are currently capped at 50 members with anticipation to increase capacity based on need and utilization if funding permits.
ACRP Membership through the organizational account immediately connects users with:

- 200-plus on-demand training, continuing education and ACRP Certification Exam preparation modules available in a Penn State College of Medicine and Penn State Health-branded learning environment
- Unlimited ACRP contact hours for ACRP certification renewal
- Breaking news and regulatory updates
- ACRP's community and members-only discussion groups
- Plus, ACRP member pricing for ACRP certification and the ACRP annual conference

Please contact Liz Galgocy at egalgocy@pennstatehealth.psu.edu (mailto:egalgocy@pennstatehealth.psu.edu) with questions, for access instructions or to be added to the waiting list for account access.

Privacy and Security Training

The institution provides a number of training opportunities to be sure our workforce members are HIPAA compliant. The courses are designed to satisfy accreditation, contractual and regulatory requirements, and they range from online courses used during New Employee Orientation, to introductory and refresher presentations available to employees through Compass. Cybersecurity and Privacy Annual Training is assigned yearly through Compass and

completion is required to maintain compliance for continued employment (login required).

Training in Dangerous Goods Shipping

Required trainings include:

- CITI (http://citi.psu.edu) Yearly Biosafety Training
- Search the COMPASS Training Link (https://launcher.myapps.microsoft.com/api/signin/fefbc74e-b2a0-4022-98df-abfa36a44562?tenantId=5dac48a7-13dd-4a80-99f6-4ae26cf3edb3) for the following required courses:
  - Safety Annual Training 100
  - Safety Annual Training College of Medicine 100
  - Biological Shipping and Dry Ice Training
  - COM Bloodborne Pathogens Training or Infection Prevention/Control Training

Other Safety Training

LAB SAFETY TRAINING OR BIOLOGICAL SAFETY, CHEMICAL/LABORATORY SAFETY, AND HAZARDOUS WASTE MANAGEMENT AND MINIMIZATION

Lab safety training is for research laboratory personnel in the Penn State College of Medicine. Every employee working in the research lab is required to take general safety training on an annual basis. Learn more on the Department of Safety section of the Infonet (https://infonet.pennstatehershey.net/web/safety/safety-training) (login required).

Annual blood-borne pathogen training is required for labs currently using unfixed human and or non-human primate materials including human derived cell lines. Learn more on the Department of Safety section of the Infonet (https://infonet.pennstatehershey.net/web/safety/bloodborne-pathogens-exposure-control-plan) (login required).

SAA (Satellite Accumulation Area) training is required for each laboratory to have a representative registered and trained in the hazardous waste disposal and minimization program. Learn more on the Department of Safety section of the Infonet (https://infonet.pennstatehershey.net/web/safety/) (login required).

CITI Biosafety/Biosecurity training is required by the Principal Investigator if operating a lab on the College of Medicine campus. The training is highly recommended for all laboratory personnel including technicians, technologists, postdoctoral scholars and visiting scientists. See more information at citi.psu.edu (https://citi.psu.edu/).

VIEW MORE INFORMATION ABOUT RESEARCHING COMPLIANCE TRAINING REQUIREMENTS (/RESEARCH-SUPPORT/RESEARCH-QUALITY-ASSURANCE/TRAINING/)

CATS IRB and STAR System Training

New Submitter Training is conducted by the IRB for submissions to the Centralized Application Tracking System Institutional Review Board (CATS IRB). This orientation provides detailed training on the ethical principles of human research, an explanation of the researcher's primary responsibility for protecting research subjects and for complying with all applicable provisions of institutional, state and federal laws. It provides an explanation of the different levels of IRB review and describes the processes for IRB submissions. Find upcoming IRB trainings and workshops (https://www.research.psu.edu/education). The clinical trials management system, **Study Tracking and Analysis for Research (STAR)**, training is provided by the CTO. Learn more on the STAR Infonet section (https://infonet.pennstatehershey.net/web/study-tracking-analysis-for-research/training-resources) (login required). There may be additional training requirements based on your departmental requirements.

Coverage Analysis and Internal Budgets

Information pertaining to Payer Coverage Analysis and clinical trial budgeting is available through the Clinical Trials Office (https://research.med.psu.edu/research-support/clinical-trials-office/coverage-analysis/).

Financial Conflict of Interest Training

All investigators who are engaged in research must complete Penn State University's required FCOI training and submit a disclosure of significant financial interest. Per PSU Policy RP06, an investigator is defined as: "any individual, regardless of his or her title or position, whether faculty, staff, or student, who has the ability to make independent decisions related to the design, conduct or reporting of University Research, but not including individuals who perform only incidental or isolated tasks related to a University Research project." Disclosure is required prior to the submission of an application for research funding, at least annually, and within 30 days of the discovery or acquisition of a new Significant Financial Interest. The Disclosure must identify significant financial interests of the investigator, spouses/partners, and dependent children that exceed the thresholds set by PSU and that relate to any of the investigator's institutional responsibilities. Additionally, the College of Medicine has specific disclosure requirements for financial interest related to either human subjects research or purchasing responsibility. Both FCOI training and disclosure are completed via Penn State University's electronic Conflict of Interest System, COINS (coins.psu.edu (https://coins.psu.edu)). As part of the electronic Disclosure Form, COINS requires investigators to complete FCOI training upon their first disclosure and again every four years. For details, please see the College of Medicine Conflict of Interest Program Overview (https://research.med.psu.edu/research-support/conflict-of-interest/) and PSU Policy RP06 Disclosure and Management of Significant Financial Interests (https://policy.psu.edu/policies/RP06).

Non-Penn State Health Researchers Conducting Research On-Site At Penn State Health/Penn State College of Medicine

There are additional requirements for when a Penn State research project includes research procedures on-site in a Penn State Health or Penn State College of Medicine facility, and the onsite study team includes employees of Penn State who are not specifically a student or employee of the health system or College of Medicine. These requirements are not related to research, and do not apply to study team members that will never be in person at a Penn State Health or College of Medicine facility. These requirements are driven by the health system and requirements from the joint commission, the

accrediting body for US health care organizations and programs. The joint commission requires that the exact same standards be applied to “all members of the workforce.” Anyone working on site at Penn State Health or Penn State College of Medicine for 5 or more days is considered a member of the workforce and must complete the same clearances as regular employees on campus.

View information related to the requirements and related guidance when these circumstances exist (https://pennstateoffice365.sharepoint.com/:w:/s/COMweb/EdGhUWOt36pImwHi3sYmnSABD-2pUE0vqt_g2sKgoGDClQ) (in Sharepoint; Penn State Access ID login required).

Finding Collaborators

The Penn State Research Portal (Pure) (https://pure.psu.edu) is a publicly-available system that captures and displays the research output of the University, both for investigators and units, and facilitates collaboration between investigators across the University and beyond. Pure is one of several applications by the company Elsevier. Pure aggregates research information from internal and external sources and enhances the visibility and discoverability of research at Penn State, both internally and externally. It provides detailed information on scholarly output, publications, networks, citation data from journals and social media citations. See details about Pure here (https://research.med.psu.edu/pure).

For further information, resources, and assistance in identifying collaborators and funding opportunities, please also visit the Research Development website (https://research.med.psu.edu/research-support/research-development/).

Research Administration Support Offices

There are multiple central research administration support offices throughout the organization. Click on each link provided for information regarding each of these offices.

- Center for Medical Innovation (CMI) (/departments/medical-innovation)
- Clinical Trials Office (CTO) (/cto)
- Human Research Protection Program (HRPP) (/https://www.research.psu.edu/irb)
- Penn State Clinical and Translational Science Institute (CTSI) (https://ctsi.psu.edu)
- Office of Research Affairs (ORA) (/ora)
- Research Development (/research-support/research-development)
- Research Quality Assurance (RQA) (/rqa)

Study Development and Feasibility: CTSI Resources

CTSI Assistance Overview

Penn State Clinical and Translational Science Institute (CTSI) can provide a wide range of consultation services during all stages of studies, and specifically during the project development and start-up phases. The new Research Navigator service provides hands-on support in conducting research. See CTSI consultation services (https://ctsi.psu.edu/consultations) and request Research Navigator assistance.

Clinical Trials Resources

The mission of the College of Medicine Clinical Trials Office is to enhance, foster and promote organized, high-quality clinical research within Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine.

By promoting clinical research, the Clinical Trials Office helps Penn State Health and Penn State College of Medicine meet its mission goals of excellence in patient care, education, research and community service.

Established in the 1990s, current services offered to support investigators include protocol and budget feasibility assessment, budget preparation and negotiation, regulatory and IRB submission and oversight, study coordinator services and clinical trial placement.

Learn more about the Clinical Trials Office (/cto).

Biostatistics

Biostatistics support is provided by the Division of Biostatistics and Bioinformatics in the Department of Public Health Sciences. Statisticians can assist researchers with all sizes and types of projects, from simple data analyses to large multi-center clinical trials. Specific services include grant proposal preparation, study design/sample size calculation, development of a statistical analysis plan, data analysis and interpretation, manuscript review and preparation, response to reviewer comments and statistical advice only. Learn more and access the consultation form on the CTSI website (https://ctsi.psu.edu/consultations/).

Clinical Research Center (CRC)

The Clinical Research Center (CRC) (https://research.med.psu.edu/research-support/crc/) provides clinical research resources and expertise to investigators who conduct research with human subjects. The 6,800-square-foot CRC in Hershey is located on the fourth floor of Penn State Health Milton S. Hershey Medical Center and includes clinical exam rooms, private subject beds, procedure space, an observational study suite, consultation space, infusion sleep rooms, negative pressure rooms, DXA scanner and specimen processing and storage space. The unit is staffed by research nurses who implement protocol-specific requirements including drug administration, timed blood draws, electrocardiograms and assistance with various study-related procedures. They are certified in chemotherapy/biotherapy administration. CRC nursing is available 7:30 a.m. to 4 p.m. Monday-Friday. Nursing assistance may be available outside of these times with adequate notice. The unit is available by badge access to investigators and their study teams 24 hours a day.

The Exercise Research Center (ERC) is a 4,500-square-foot, state-of-the-art facility conveniently located at the Hershey Center for Applied Research (HCAR) for easy access for participants. Resources include four separate testing areas, a reception and waiting area, exam room and secure file room. The Exercise Research Center has a fee-for-service basis and provides highly skilled and trained exercise physiologists and CRC nursing support to

conduct body composition and exercise assessments.

Body Composition equipment includes:

- DXA scanner
- Resting metabolic analyzer
- Bioelectrical impedance analysis (BIA)
- Skinfolds
- Anthropometric measurers
- BODPOD

Exercise Physiology equipment includes:

- Metabolic gas analysis system
- EKG system
- Biodex dynamometer
- Multistation resistance training unit
- Strength training equipment
- Pulmonary function tests
- Treadmills, bikes and arm ergometers

Clinical Research Nurses: Highly skilled clinical research nurses implement protocol-specific procedures and provide direct nursing care for all subjects enrolled in research studies. CRC nurses are committed to subject safety and protocol fidelity. CRC nurses are certified in chemotherapy administration, conscious sedation and ACLS. Learn more about the CRC (https://research.med.psu.edu/research-support/crc/) and request a consultation with the CRC.

Research Ethics

The Research Ethics Consultation Service is a free service available to all biomedical researchers at Penn State who seek advice regarding ethically complex aspects of their biomedical research. Learn more on the CTSI website (https://ctsi.psu.edu/consultations/).

Community Engagement

The Community Engagement Consultation Service provides opportunities for researchers and community members interested in healthcare research to get expert feedback on how to engage communities around research ideas, proposals, evaluations, and ongoing projects. Learn more on the CTSI website (https://ctsi.psu.edu/consultations/).

CHEER – THE COMMUNITY HEALTH EQUITY & ENGAGEMENT IN RESEARCH PROGRAM

CHEER is a partnership between the Social Science Research Institute (https://ssri.psu.edu/) (SSRI) and the Clinical and Translational Science Institute (https://ctsi.psu.edu/) (CTSI) at Penn State. The CHEER program promotes community-engaged research (CEnR) across Penn State, spanning many disciplines, with the overall goal of enhancing wellness and reducing health disparities. It serves as the landing place for faculty who seek to engage communities in their research and for community organizations and members to engage with Penn State (https://www.psu.edu/) expertise. The CHEER team is here to jumpstart your career in CEnR, connect you with community partners based on shared interests, and provide resources and educational programming in an effort to promote meaningful and sustainable partnerships.

The CHEER Researcher Toolkit (https://ctsi.psu.edu/cheer/researcher/introduction/) is designed to educate learners about the importance of community-engaged research (CEnR), guiding CEnR principles to support meaningful engagement and strategies to develop and maintain successful community-academic partnerships. Weaved throughout each section are real-world, evidence-based best practices and resources.

Biomedical Informatics

REDCap (Research Electronic Data Capture) is a secure web application for building and managing online surveys and databases. It is a novel workflow methodology and software solution designed by Vanderbilt University for rapid development and deployment of electronic data capture tools to support clinical and translational research. Using REDCap's streamlined process for rapidly developing projects, you may create and design projects using:

- the online method from your web browser using the Online Designer
- the offline method by constructing a "data dictionary" template file in Microsoft Excel, which can be later uploaded into REDCap

Both surveys and databases (or a mixture of the two) can be built using these methods. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R). Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields. REDCap has a quick and easy software installation process, so that you can get REDCap running and fully functional in a matter of minutes. Learn more about REDCap on the CTSI website (https://ctsi.psu.edu/redcap). The staff of the Data Management Unit at the Department of Public Health Sciences offers REDCap configuration services to allow investigators to more easily develop and implement a fully operational and customized REDCap project based on the needs of their study. Services include:

- REDCap project design (*e.g.,* longitudinal studies and cross-sectional surveys)
- Development of case report forms, data entry forms and surveys
- Creation of REDCap randomization models as well as backup randomization processes
- Creation of data quality rules and data flow processes
- Customization and implementation of study's Electronic Regulatory Binder

Trial Innovation Network (TIN) and Penn State Hub Liaison Team

The Trial Innovation Network is a new collaborative initiative within the Clinical and Translational Science Awards (CTSA) Program and is composed of three key organizational partners – the CTSA Program Hubs, the Trial Innovation Centers (TICs), and the Recruitment Innovation Center (RIC). All are key partners of the Trial Innovation Network and make unique and essential contributions. Other important partners include NIH institutes, other federal and non-federal stakeholders, researchers, patients, providers and the public. The local Penn State Hub Liaison Team works together to provide support and resources for investigators to develop proposals into protocols, optimize study operations, and enhance recruitment and enrollment. Investigators must contact their local Trial Innovation Liaison Team to discuss their proposal and obtain a brief consultation prior to submission. A consultation with the local Trial Innovation Liaison Team is important because these teams will directly connect the local hubs to the national network and provide advice and input on proposals. Learn more on the CTSI website (https://ctsi.psu.edu/research-support/clinical/#question_trialinnovationnetwork) and the Trial Innovation Network national site (https://trialinnovationnetwork.org/).

Exercise Research Center (ERC)

The Exercise Research Center provides space, equipment and trained personnel to Penn State investigators. Resources include unique facilities and equipment, as well as highly experiences staff who are trained in human subjects' protection, good clinical practices, protocol implementation and compliance. The facilities are approximately 4,500 square feet and include a DXA scanner, resting metabolic rate system, BODPOD, anthropometric measures, skinfold calipers and bioelectrical impedance analysis. Exercise testing equipment includes stationary and portable VO2 metabolic systems, a Biodex, resting ECG, treadmills, weight machines, bikes and a multi-station, resistance training unit.

Exercise Physiologist: A highly skilled exercise physiologist staffs the ERC and can provide oversight of all of the tests that can be conducted at the facility. The ERC exercise physiologist is committed to subject safety.

Learn more about the Exercise Research Center (https://research.med.psu.edu/research-support/crc/#question_exerciseresearchcenter) on the Clinical Research Center website (https://research.med.psu.edu/research-support/crc/).

Study Development and Feasibility

Assessment of Potential Cohort for Feasibility or Recruitment

A pool of potential study subjects can be estimated using TriNetX. Through TriNetX, users search for patients meeting specified criteria in a de-identified database, without prior Institutional Review Board (IRB) approval. Data are presented as unique patient counts, and a patient is counted only once. Data in TriNetX also exclude patients with only a medical record number or without diagnoses or codes. Such a search can help researchers determine whether enough potential patients are available to properly conduct a research study. With IRB approval and an enterprise information management request, patient-level data can be requested.

TriNetX also offers chart and graph options for data visualization and includes a rate-of-arrival algorithm. This algorithm determines how many patients matching certain criteria visited Penn State Health within the past three years, and then predicts how many potential visits will happen each quarter over the next year. A Trial Connect feature allows clinical research organizations and industry sponsors to determine and connect with potential study sites.

Learn more at Penn State Clinical and Translational Science Institute's website (https://ctsi.psu.edu/trinetx).

Requesting Access to Protected Health Information (PHI) Data for Preparatory Research

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. In order to gain access to the PHI, the principal investigator needs to demonstrate that the use or disclosure of the protected health information is solely to prepare a research protocol or for similar purposes preparatory to research, that the researcher will not remove any protected health information from the covered entity, and representation that protected health information for which access is sought is necessary for the research purpose. Submit the Review Preparatory to Research Attestation Form (https://forms.office.com/r/XUqCghfpdY) for IRB for review and approval. For more information about the Privacy Rule and preparatory to research provisions go to: 45 CFR 164.512i, paragraph (1)(ii) of the definition of "protected health information."

In order to remain compliant with the privacy laws, investigators are strongly encouraged to utilize de-identified data, when possible, and access such data through TriNetX. Investigators do not need to file this form to access de-identified data through TriNetX (https://ctsi.psu.edu/trinetx).

For all preparatory requests, the following rules apply:

- The investigator must attest that the work is solely to review PHI to prepare a research protocol or for similar purposes preparatory to research.
- The investigator must provide a statement affirming that no PHI will be removed from the covered entity by the researcher in the course of the review. This means that the data retrieved cannot be shared, in an identifiable fashion, with any person or third-party agency.
- The investigator may only access the information necessary to reach their research goals in accordance with the Minimum Necessary Rule.
- The investigator must agree that any access to PHI without a signed HIPAA authorization will be tracked by the individual accessing the information.

Executing Confidentiality Non-Disclosure Agreement

This activity is required for industry-sponsored clinical studies and investigator-initiated clinical studies with funding from industry. In many instances a sponsor sends a Confidential Disclosure Agreement (CDA) prior to sharing a protocol or confidential documents. If a CDA is not provided by industry, a PI may request that the Office of Research Affairs send a CDA to the industry representative. If a PI receives a CDA or would like to send a CDA, the request should be submitted via this online form (https://apps.sims.psu.edu/NDA/Assurance.aspx) (Penn State Access ID login required). The Office Research Affairs reviews CDAs in great detail and ensures that it complies with the Penn State Health and Penn State College of Medicine rules for confidentiality, data retention and information ownership. CDAs require an authorized signature of Penn State College of Medicine, as well as a signature from the PI acknowledging the confidentiality obligations. See the "Submitting Contracts for Approval" section of this guidebook for other industry contract-related activities.

Clinical Trials Grant Preparation Service

The Department of Medicine, under the direction of Dr. Christopher Sciamanna, operates a grant preparation service for investigator-initiated clinical trials. The group works with faculty who are at the point in their career where they have some pilot data, a compelling clinical trial question to answer and the ability to do the work if funded. The team includes a PhD with experimental research training who works closely with Dr. Sciamanna and a grants management specialist to address budgetary and other grant requirements. This is not solely a grant preparation service and works closely with investigators to help them design the trial so that it has the greatest possible chance of external funding. This group focuses the grants toward large federal funders (NIH, PCORI, etc) but is not opposed to other sources, assuming they are large enough to conduct a properly powered clinical trial. The first step to using this service is to speak to Dr. Sciamanna (cns10@psu.edu (mailto:cns10@psu.edu)). The group works with investigators in departments other than Medicine, and the service has been operational since 2016.

Data and Biostatistics Support from the Department of Public Health Sciences

The Department of Public Health Sciences has been serving as a data coordinating center for NIH-funded multi-site clinical trials since 1993. Through this experience, the department has developed the following areas of expertise:

- Data management
- Biostatistics
- Research computing
- Project management

After consulting with you and assessing the scope of the project, an experienced individual, or a full team of qualified researchers, can be assigned to work with you to efficiently handle all aspects of your project. Services include protocol development, project management (both administrative and clinical), forms development, data management, REDCap development, custom application development, IND/IDE submissions, manual of operations (MOP) development, statistical consultations, and snalysis and manuscript preparation and review. Learn more about services from the Department of Public Health Sciences (https://med.psu.edu/phs/services).

Some no-cost support is available through the Biostatistics, Epidemiology and Research Design (BERD) core within the Clinical and Translational Science Institute (CTSI). Request a consultation for all BERD services here (https://app-phs.hmc.psu.edu/walkin2/forms/walkin_form.cfm).

Monitoring Plans

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirement(s).

Typically, academic sites are familiar with monitors assigned by a sponsor or a contract research organization (CRO). However, GCP requires that investigator-initiated trials enrolling human subjects also provide a monitoring plan to assure that the data collected throughout the study are accurate. In addition, the Code of Federal Regulations requires monitoring under 21CFR 312 subpart D (for INDs) and 21CFR 812 subpart C (for IDEs).

Sponsors (including Sponsor-Investigators) of clinical investigations conducted under an IND or IDE are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to FDA.

This oversight is maintained through the regular review of the source data, case report forms, informed consents, regulatory documents and any other essential documents by a monitor.

During a monitoring visit, a monitor reviews individual subject records and source documents, regulatory binder(s), and other essential documents and compares the information with data recorded on the case report forms (CRF) or entered in the electronic case report form (eCRF).

The monitor is obligated to ensure the following:

- Subjects meet eligibility requirements
- The rights and safety of human subjects are protected
- Informed consent has been obtained and documented appropriately
- Conduct of trial is in compliance with protocol, good clinical practice (GCP), and applicable regulatory requirements
- Subject was followed and treated according to the protocol
- Reported trial data are accurate, complete, and 100% verifiable from source documents; all pertinent information in the subject records must be accurately recorded on the CRF
- The CRF is complete, legible, and consistent throughout visits

Typically, in an industry-sponsored study, the pharmaceutical company will provide the monitor for the study. However, in the case of a study conducted by a Sponsor-Investigator, the Investigator takes on the responsibility of ensuring that the study is being monitored.

For industry-sponsored studies a monitoring plan will often be used to guide the frequency of monitoring visits to investigative sites whereas in an Investigator-initiated study the Investigator and/or study staff should develop a monitoring plan.

The frequency of visits is affected by the complexity of the study and the rate of enrollment. Monitoring plans can be updated during the course of the study if, for example, enrollment is faster than expected. When a monitor comes to a clinical site to conduct a monitoring visit, they will need access to all source documents, including the Electronic Medical Record (EMR).

Learn more about the process for requesting monitoring access to the EMR via the Clinical Trials Office (/cto).

Public Health Sciences (PHS) Clinical Trial Monitoring

Clinical Trial Monitoring Services are required by Penn State College of Medicine Institutional Review Board (IRB) and Research Quality Assurance (RQA) offices for investigational drug/devices (IND/IDE), multisite and high-risk clinical trials. The Data Management Unit of the Department of Public Health Sciences receives institutional support to provide no-cost monitoring services, as directed by the IRB and RQA offices, to Penn State investigators conducting clinical research. Additionally, budget estimates can be prepared for other types of human subject research interested in data monitoring services. Estimates should be obtained early in the protocol development and feasibility process. Clinical Trial Monitoring services provided by the Data Management Unit help the investigator ensure that:

- All clinical trial activities follow the research protocol

- Participants' rights, welfare, and safety are protected
- Quality, reliability, and integrity of data collected are maintained throughout the study
- Liability risk to the institution is minimized

Services include:

- Creation of a customized data monitoring plan
- Source document verification
- Review of regulatory documents
- Tracking of investigational products
- Data monitoring visits

See the Department of Public Health Sciences for details (https://med.psu.edu/phs/services).

DSMB/C (If Required)

This section describes the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) (also known as Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs) that may carry out important aspects of clinical trial monitoring. A clinical trial Data Monitoring Committee is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the investigator regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. DMCs have the practical position of seeing data and safety information in more frequent intervals and with typically more statistical expertise to make enhanced assessments about a study's progress and determine the study's future.

DMC/B: WHAT DO THEY DO?

DMC/Bs perform the following general functions:

- Objectively appraise a study's progress
- Assess data quality via a formal and planned process
- Provide analytical expertise and rigor
- Determine the statistical significance of efficacy and/or risk-benefit ratio
- Serve as "another set of eyes"

In accordance with its analytic and ethical responsibilities, a DMC is tasked to determine whether a study can proceed with enrollment, as designed. It has the authority to halt a study, suspending enrollment, pending crucial changes to the protocol's design, recruitment strategy, risk minimization, or other modification. It can also terminate a study due to statistically significant efficacy or increased risk of harm to participants.

DMC/BS: WHEN ARE THEY NEEDED?

A fundamental reason to establish a DMC/B is to enhance the safety of trial participants in situations, in which safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. All clinical trials require safety monitoring, but not all trials require monitoring by a formal DSMC/B. DMC/Bs are established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DMC/Bs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity. Formal data and safety monitoring is also necessary to assure confidence in a study's interim and final outcomes:

- To verify or validate efficacy and/or safety information significant to a novel therapy
- To gauge data quality to confirm the research question/ hypothesis in developing treatments
- To assess efficacy and safety when "lives and wellbeing depend on valid results"

The FDA recommends that sponsors consider using a DMC/B when:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion
- There are a priori reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive
- There is prior information suggesting the possibility of serious toxicity with the study treatment
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint
- The study is large, of long duration, and multi-center

In studies with one or more of these characteristics, the additional oversight provided by a DMC/B can further protect study participants. In other studies, such as short-term studies for relief of symptoms as noted above, such committees are generally not warranted. (FDA Guidance: The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors – Guidance for Clinical Trial Sponsors – Establishment and Operation of Clinical Trial Data Monitoring Committees (https://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm))

DMC/B CHARTERS

DMC/Bs typically operate under a written charter that includes well-defined standard operating procedures. Such charters are important for the same reason that study protocols and analytical plans are important—they document that procedures were pre-specified and thereby reduce concerns that operations inappropriately influenced by interim data could bias the trial results and interpretation. The sponsor may draft this charter and present it to the DMC/B for agreement, or the DMC/B may draft the charter with subsequent concurrence by the sponsor. Topics to be addressed would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC/B meetings, procedures for assessing conflict of interest of potential DMC/B members, the method and timing of providing interim reports to the DMC/B, and other issues relevant to committee operations. FDA may request that the sponsor submit the charter to FDA well in advance of the performance of any interim analyses, ideally before the initiation of the trial (see 21 CFR 312.23(a)(6)(iii)(g); 21 CFR 312.41(a); 21 CFR 812.150(b)(10)).

In such cases, FDA would usually consider the charter when FDA reviews the study protocol. (FDA Guidance: The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors – Guidance for Clinical Trial Sponsors – Establishment and Operation of Clinical Trial Data Monitoring Committees (https://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm))

Research Procedures using ionizing radiation Request Form

The Department of Radiology supports and encourages clinical research at Penn State Health and Penn State College of Medicine. If your protocol contains ionizing radiation procedures (standard of care and/or research-related procedures), you must complete the Radiation Review Form and include it with your IRB submission in CATS IRB. All research protocols/studies that involve non-routine radiation procedures must be reviewed by the Human Use of Isotope Committee (HUIC). It is also highly advised that you communicate with the CTO prior to starting your study or even at the protocol preparation step. CTO will work with Radiology to establish the exact process for your procedure and will provide a cost estimate. This is especially important if your experimental requirements deviate from the standard radiology procedures, i.e. require an unusual contrast agent. It is not uncommon that radiology services are not clearly detailed in the text of the protocol, potentially resulting in additional unanticipated charges at the point of service. See the Additional Approvals in the “Preparing Documents” section of this guidebook for details. HRP 903 Radiation Review Form is available in the CATS IRB library (login required).

Department of Pathology Resources

The Department of Pathology is committed to excellence in patient care, education, and translational and basic research, and plays a vital and integral role in the medical center’s multifaceted missions. Through provision of high quality diagnostic services and the practice of laboratory medicine, the department supports the wide range of medical care provided at the institution.

Find Laboratory Licenses (such as CLIA) and Accreditations via the Clinical Trials Office (/cto).

Investigators planning to use any of the following specimens in their research project must complete the Use of Human Tissue for Research Form and include it with the CATS IRB Submission:

- Collection of tissue from surgical or biopsy procedures
- Collection of bone marrow from bone marrow biopsies and/or bone marrow aspirates
- Use of archival pathologic specimens stored in Anatomic Pathology
- Collection of tissue from cadavers
- Collection of placenta specimens

The completed form is reviewed by Anatomic Pathology during IRB review. After review and approval of the proposed tissue request, the Department of Pathology will notify the investigator and the IRB. Pathology approval will be required before the official IRB approval is issued.

No tissue will be released to an investigator without approval from Anatomic Pathology. See the Additional Approvals item in the “Preparing Documents” section of this guidebook for details.

GENERAL INFORMATION ON PATHOLOGY

Any time human tissue is removed for research purposes, the specimen must pass through either the Surgical Pathology Laboratory or Autopsy Suite. Adequate diagnostic tissue will be retained in the laboratory prior to providing specimens for research. Therefore, Pathology is usually able to provide tissues from major surgical excisions but can only rarely provide tissues from small biopsies obtained for diagnostic purposes.

There is a charge per specimen to help defray the technical cost in obtaining research tissues. Please call the Department of Pathology at 717-531-8352 (tel:17175318352) for the current charge to use when preparing the budget for a grant.

If the investigator is aware that a biopsy or excision of the desired tissue is scheduled, they should complete and submit to the Anatomic Pathology Gross Room (fax to 717-531-0831) a “Research Tissue Request Form” prior to the scheduled date of surgery. This form notifies the Gross Room staff that a specimen is a potential source of research tissue so that the specimen can be handled appropriately for that purpose.

A blank copy of this form can be obtained from the Gross Room; this blank form can be photocopied for multiple submissions.

Investigational Drug Services

See the “Investigational Drug Pharmacy (IDS)” section in this guidebook for a detailed description of the Investigational Drug Services (IDS), start-up requirements and fees.

Clinical Research Biospecimen Core

The mission of the Clinical Research Biospecimen Core (https://research.med.psu.edu/core-facilities/clinical-research-biospecimen-core/) is to provide a centralized service for the processing and distribution of human subject research samples for all clinical research activities at Penn State College of Medicine and Penn State Health Milton S. Hershey Medical Center.

The goals of the Clinical Research Biospecimen Core (CRBC) are two-fold:

- First, by providing a centralized service for clinical research sample handling, more favorable study contract pricing with extramural research sponsors will be allowed.
- Second, by utilizing a centralized core service dedicated solely to this purpose, internal investigators will find it easier to budget and efficiently conduct their human subject research efforts.

IND and IDE Submissions

Overview of Regulatory Requirements for Clinical Studies Involving a Drug, Biologic or Dietary Supplement

FDA's Center for Drug Evaluation and Research (CDER) is responsible for regulating manufacturing, testing and importation of pharmaceutical drugs in the US. This includes new drug approvals, abbreviated new drug approvals (generics), over-the-counter drugs, animal drugs and biologics. A drug is defined as:

- substance intended for use in diagnosis, cure, mitigation, treatment, or prevention of the disease;
- substances (other than food)intended to affect the structure or any function of the body;
- substance intended for use as a component of a medicine but not a device or component of a device.

Other sections of this guidebook provide a brief summary of regulatory requirements for clinical research involving drugs, biologics or dietary supplements.

Preclinical Regulatory Requirements

Preclinical testing begins after a potential drug has been identified in the lab. Preclinical testing involves lab and animal studies that evaluate the drug's toxic and pharmacologic effects. Preclinical studies are also subject to the FDA regulations known as Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies, 21 CFR 58. The GLP regulations specify minimum standards in such areas as personnel, facilities, equipment and operations.

> Pre-clinical studies not performed under GLP conditions may not be accepted by the FDA. Recognition of this fact is particularly important for academic drug development. Please see "Roadmap for Academic Health Centers to Establish Good Laboratory Practice-Compliant Infrastructure", Acad. Medicine, 2012 87(3):279-284

Preclinical testing includes pharmacokinetics, the study of how the drug moves through living organisms. Researchers examine absorption, distribution, metabolism and excretion (also abbreviated as ADME) to ensure that the drug reaches its intended target and passes through the body properly. In addition to the biological tests, researchers conduct chemistry tests to establish the drug's purity, stability and shelf life. Manufacturing tests are conducted to determine the feasibility of producing the drug on a large scale and to explore dosing, packaging and formulation (e.g., pill, inhaler, injection). At the preclinical stage, the FDA will generally ask, at a minimum, that sponsors:

- develop a pharmacological profile of the drug;
- determine the acute toxicity of the drug in at least two species of animals, and
- conduct short-term toxicity studies ranging from two weeks to three months, depending on the proposed duration of use of the substance in the proposed clinical studies.

FDA Guidance for Industry: See Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htn

Investigational New Drug (IND) Application (21 CFR Part 312)

After preclinical testing is completed, a sponsor or sponsor-investigator (see below) files an IND with FDA prior to beginning any human testing. An IND is a request for FDA authorization to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any unapproved drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. The application must show results of preclinical experiments; the chemical structure of the compound; how it is thought to work in the body; any side effects found in animal studies; and how the compound is manufactured (chemistry, manufacturing and controls section). The IND must also include a detailed clinical trial plan, including how, where and by whom the studies will be conducted. Based on the information of the IND application, the FDA will determine if there is sufficient evidence to support initial human testing. The sponsor must wait 30 days after submitting the IND to the FDA for review. At the end of the 30 day review period, unless the FDA identifies a potential safety problem involving the use of the drug and asks for a delay, the sponsor may begin the proposed clinical testing. Per Penn State University Policy RP-05 "Research Quality in Human Participant Research," it is required that the Research Quality Assurance (RQA) group be contacted to provide support for the submission process for INDs or IND Exemptions, and to perform an administrative review of the submission prior to being sent to the FDA. See Penn State University policy (https://policy.psu.edu/policies/RP05).

Expanded Access to Investigational Drugs

The terms "expanded access," "compassionate use," "treatment use" and "treatment IND" are used interchangeably to refer to use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. Investigational drugs are new drugs that have not yet been approved by the FDA or approved drugs that have not yet been approved for a new use, and are in the process of being tested for safety and effectiveness. The distinction between administering an investigational drug in the setting of a "traditional" clinical trial versus expanded access lies in the intention. In a traditional clinical trial the intention is to understand the safety and effectiveness of the investigational drug; in expanded access the intention is treatment. There are four general guidelines for a drug to be considered for expanded-access use:

- Patients with a serious or immediately life-threatening disease or condition, where there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition.
- No comparable or satisfactory alternative therapy exists.
- The potential patient benefit justifies the potential risks of the treatment, and those risks are not unreasonable in the context of the disease or condition being treated.
- The expanded use of the investigational drug for the requested treatment will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the product.

The Human Research Protection Program (HRPP) should be contacted (https://www.research.psu.edu/irb) for further guidance as soon as a provider is considering using an investigational drug under any expanded access condition. See FDA details on expanded access (https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm).

New Drug Application (NDA)

After clinical trials have been completed demonstrating safety and effectiveness, the study sponsor (or drug manufacturer) will submit a New Drug Application (NDA) to the FDA for a license to market the drug for a specified indication. NDAs contain all of the information about all of the studies, including preclinical testing, all clinical trials, dosing information, manufacturing details and proposed labeling for the new medicine. Most academic drug development efforts do not progress to this stage. At NDA submission stage, FDA scientists review all the results from all the studies carried out over the years and determine if they show that the medicine is safe and effective enough to be approved. During this review, the FDA determines what the labeling should be and whether the sponsor can manufacture it properly and consistently. Once the drug is approved, it becomes available for physicians to prescribe for the indication approved by the FDA. The review process takes approximately 18 months.

Determining if your Study is Exempt from IND Requirements

Many academic investigators will want to conduct a clinical study with an already approved drug. This is often done to establish efficacy in a new disease indication. FDA provides provisions for conducting studies of lawfully marketed drugs through the use of an IND exemption. A clinical investigation of a drug is exempt from the IND requirements if all of the criteria for an exemption in 21CFR312.2(b) are met:

- The drug product is lawfully marketed in the United States;
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
- The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product;
- The investigation 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 investigation will be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50;
- The investigation will be conducted in compliance with FDA regulations 21 CFR 312.7: Promotion of investigational drugs.

Thorough documentation is required to support this exemption criterion and may include prior publications or other public disclosures. If such evidence cannot be provided, a physician should submit a research IND (limited in scope) to the FDA. The physician is now considered sponsor-investigator. **FDA Guidance:** See Investigational New Drug Applications (INDs) – Determining whether Human Research Studies can be conducted without an IND (https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm36274
Per Penn State University Policy RP-05 “Research Quality in Human Participant Research,” it is required that the Research Quality Assurance (RQA) group be contacted to provide support for the submission process for INDs or IND Exemptions, and to perform an administrative review of the submission prior to being sent to the FDA. See Penn State University policy (https://policy.psu.edu/policies/RP05).

Is IND Required for Studies with Dietary Supplements?

Many clinical studies of academic investigators evaluate the effect of dietary supplements on the disease or physiological parameters. Some of these studies may require an IND submission. If the dietary supplements are investigated for diagnosis, cure, mitigation, treatment, or prevention of disease and are used to affect the structure or function of the body, then the dietary supplement will be considered a drug for the purposes of this study. The study will be the subject to the same regulations as any other unapproved drug. Specifically, the FDA will be paying particular attention to the composition of the dietary supplement, its origin and manufacturing processes. When preparing the INDs for dietary supplements, make sure that the supplement manufacturer is willing to provide this information. **FDA Guidance:** See Investigational New Drug Applications (INDs) – Determining whether Human Research Studies can be conducted without an IND (https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm36274

Regulatory Requirements for Clinical Studies with Devices

FDA’s Center for Devices and Radiological Health (CDRH) is responsible for regulating manufacturing and importation of medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, X-ray systems, ultrasound equipment, microwave ovens and color televisions.

If a product is labeled, promoted or used in a manner that meets the definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act, it will be regulated as a medical device.

A device is: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,” or
- “intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

This definition provides a clear distinction between a medical device and other FDA regulated products such as drugs. If the primary intended use of the product is achieved through chemical action or by being metabolized by the body, the product is usually a drug. In cases where it is not clear whether a product is a medical device the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) can assist in making a determination.

FDA Guidance: See Frequently Asked Questions about Medical Devices (https://www.fda.gov/files/about%20fda/published/Frequently-Asked-Questions-About-Medical-Devices---Information-Sheet.pdf).

See details via the Clinical Trials Office (/cto).

Device Classification

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes (Class I, Class II and Class III) based on the level of control necessary to assure the safety and effectiveness of the device.

The device classification defines the regulatory requirements for an approval of a new device. Regulatory control increases from Class I to Class II to Class III. Device classification depends on the intended use of the device and also upon indications for use. In addition, classification is risk-based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned.

Examples:

- **Class I devices:** elastic bandages, examination gloves and hand-held surgical instruments.
- **Class II devices:** powered wheelchairs, infusion pumps and surgical drapes.
- **Class III devices:** implantable pacemaker pulse generators and coronary stents.

To find the classification of a device, as well as whether any exemptions may exist, the classification regulation number should be determined for the device. One of the ways to accomplish this is to go directly to the FDA classification database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm) and search for a part of the device name. Once the correct classification regulation has been identified, go to the device panel (medical specialty) to which the device belongs (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051530.htm).

The search will provide the Device Classification and the appropriate CFR regulation for the device. If the device is not classified, similar devices can be researched on the FDA website (PMA and 510(k) databases) or pre-IDE consultation can be used for the FDA determination. The CTO has additional device information specific to our Medicare Administrative Contractor (MAC), Novitas Solutions, Inc.

See details via the Clinical Trials Office (/cto).

Significant Risk vs Non-Significant Risk

Devices used on human subjects to conduct investigations of safety and effectiveness are considered “Investigational Devices” (Section 520(g) of FD&C Act). Significant Risk (SR) device presents a potential for serious risk to the health, safety and welfare of a subject, and:

- Intended to be used as an implant
- Purported to support or sustain human life
- Is used for substantial importance in diagnosing, curing, mitigating or treating disease, or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Examples of SR devices include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants. Conversely, non-significant risk (NSR) device studies do not pose a significant risk to patients. Non-significant risk should not be confused with “minimal risk,” a term used by the FDA to classify studies. Examples of NSR devices include most day-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters. SR devices must meet all regulatory requirements set in 21 CFR 812, including the requirement for approval by both IRB and the FDA before commencing the study. Significant risk devices require submission of an investigational device exemption (IDE) to CDRH. NSR device studies may commence without FDA approval, based solely on the IRB approval. However, the sponsor-investigator must follow abbreviated IDE requirements, which are, in essence, the same requirements as regular IDE only without FDA submission (21 CFR 812.2 (b)). The IRB acts as a surrogate overseer for the FDA. **FDA Guidance:** See Significant Risk and Non-significant Risk Medical Device Studies (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm).

Investigational Device Exemption (IDE) (21 CFR Part 812)

Important: Clinical study of a new indication or new patient population for an already marketed device falls under the IDE regulations. Per Penn State University Policy RP-05, “Research Quality in Human Participant Research,” it is required that the Research Quality Assurance (RQA) group be contacted to provide support for the submission process for IDEs or Study Risk Determinations, and to perform an administrative review of the submission prior to being sent to the FDA. See Penn State University policy (https://policy.psu.edu/policies/RP05). An investigational device exemption (IDE) is a regulatory submission to the CDRH. If approved, it allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. IDE requirements:

- Study approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
- Informed consent from all patients obtained and documented;
- The device is labeled “CAUTION- Investigational Device. Limited to investigational use only;”
- Sponsor-investigator complies with monitoring requirements;
- Records and reports are maintained;
- Investigator cannot promote or commercialize (charge for) the device.

FDA Guidance: See Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm572934.htm). Two important elements of the guidance are:

- FDA approval of an IDE application for an early feasibility study, including some first-in-human studies, may be based on less nonclinical data than would be expected for other types of studies (e.g., traditional feasibility or pivotal).
- The introduction of new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study, while still maintaining compliance with the IDE regulations in 21 CFR 812:
    - more types of modifications that can be made under a 5-day notification without prior FDA approval, as compared with other types of studies;
    - a contingent approval process that permits changes contingent upon acceptable
    - nonclinical test results without requiring additional FDA action; and
    - interactive review of IDE supplements and amendments.

Abbreviated IDE

Studies of non-significant risk devices are subject to abbreviated IDE requirements. An IDE submission to the FDA is not required under the abbreviated requirements, but the requirements for labeling, IRB approval, informed consent, monitoring, records, reports and promotional practices contained in FDA regulations still apply (21 CFR 812.2(b)). In addition, the concept of “non-significant risk” to determine whether abbreviated IDE procedures are appropriate should not be confused with “minimal risk” to determine whether expedited IRB review is appropriate. For a device study to be eligible for expedited IRB review, it must be a non-significant risk device AND present no more than minimal risk to the subject (ref. 21 CFR 56.110). **Requirements under abbreviated IDE:**

- The sponsor will label the device in accordance with 21 CFR 812.5.
- The sponsor will obtain and maintain IRB approval throughout the investigation as a nonsignificant risk device.
- The sponsor will ensure that each investigator participating in an investigation of the device obtains and documents consent from each subject under the investigator’s care according to 21 CFR 50, unless documentation is waived by an IRB.
- The sponsor will comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations.
- The sponsor will maintain the records required under 21 CFR 812.140(b) (4) and (5) and make the reports required under 21 CFR §812.150(b) (1) – (3) and (5) – (10); The sponsor will ensure that participating investigators will maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7).
- The sponsor will comply with the prohibitions in 21 CFR 812.7 against promotion and other practices.

IDE Exemptions

Some studies may be exempt from the IDE regulations. The exemption criteria is explained in 21 CFR 812.2(c), and briefly summarized here:

- A legally marketed device when used in accordance with its labeling;
- A diagnostic device, if it is:
  - noninvasive;
  - does not require an invasive sampling procedure that presents significant risk;
  - does not by design or intention introduce energy into a subject;
  - and is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.
- Consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
- A device intended solely for veterinary use;
- A device shipped solely for research with laboratory animals;
- A custom device as defined in 812.3(b).

Emergency Use of Unapproved Device

An unapproved medical device is a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval or an approved IDE. Emergency use is permitted if the treating physician determines that:

- The patient has life-threatening condition that needs immediate treatment
- No generally acceptable alternative treatments exist
- Because of an immediate need to use the device, there is no time to use existing procedures to get FDA approval

Next, the treating physician needs to undertake the following protective measures:

- An independent assessment by an uninvolved physician
- Informed consent from the patient or legal representative
- Clearance from the institution as specified by their policies
- Approval of the IRB Chair
- Approval from the IDE sponsor, if an approved IDE exists for the device
- Prior FDA approval for shipment or emergency use of the investigational device is not required, but the use should be reported to the FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use.

Note that if a physician who is faced with an emergency situation contacts the FDA to discuss their patient’s condition, in this situation the FDA will only act in an advisory role, rather than in an approving role. The responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician. **FDA Guidance:** See Emergency Use Authorization of Medical Products (https://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm). See detailed guidance about what to submit to the IRB/HSPO (/research-support/irb-hspo/#question_emergencyusesubmissioninstructions).

Compassionate Use of Investigational Devices

This type of use is **not** an emergency use. The compassionate use (or Single Patient/Small Group Access) provision allows access for patients who do not meet the requirements for inclusion in a clinical investigation but for whom the device may provide a benefit in treating and/or diagnosing their disease or condition. This provision is typically approved for individual patients but may be approved to treat a small group. Compassionate use requires the submission by the sponsor or investigator of an IDE Supplement as per 21 CFR 812.35 requesting approval in order to treat the patient(s). In order to permit this use, FDA will review the following information:

- The patient’s condition and the circumstances necessitating treatment
- Whether comparable alternative treatment exists, and the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
- The protocol to be followed, or deviations from the approved clinical protocol that may be needed in order to treat the patient

- The patient protection measures that will be followed (informed consent, concurrence of IRB chairperson, clearance from the institution, independent assessment from uninvolved physician, authorization from IDE sponsor)
- Whether the preliminary evidence of safety and effectiveness justifies such use
- Whether such use would interfere with the conduct of ongoing clinical investigations

The investigator should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances.

Treatment Use

This type of use is **not** an emergency use. A request for Treatment Use of an investigational device in the mitigation, diagnosis and treatment of a serious disease requires a Treatment IDE Submission as per 21 CFR 812.36. If approved, Treatment IDE enables a wider group of patients to receive the investigational device for the same indication as it is being studied under the sponsor IDE. During the course of the clinical trial, if the data suggests that the device is effective, then the trial may be expanded to include additional patients with life-threatening or serious diseases. Treatment IDE will remain open even after the sponsor trial has been completed. The following provisions have to be met:

- Life-threatening or serious disease or condition
- Device is investigated in a controlled clinical trial under IDE for the same use
- Sponsor is actively pursuing market approval
- No comparable alternative treatment exists
- The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed.

PMA vs 510(k)

Premarket approval (PMA) (21 CFR 814.39) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, FDA requires sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). The content of PMA is similar to the NDA for new drugs, and contains manufacturing sections, pre-clinical laboratory studies and clinical investigations. Some devices (from Class I or Class II) may be able to be cleared under a different pathway referred to as premarket notification, or 510(k). The name refers to requirements outlined in section 510(k) of Food, Drug and Cosmetics Act. If the device is considered to be substantially equivalent to one or more similarly marketed devices (known as “predicate” devices), a claim of substantial equivalence can be made. A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design and other parameters.

Humanitarian Use

A Humanitarian Use Device (HUD) is a “medical device intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year.” (21 CFR 814). The request for HUD designation is described in the following FDA guidance: Humanitarian Use Device (HUD) Designations (https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/ucm563286.htm). The first step in seeking marketing approval of a HUD involves obtaining HUD designation of the device from FDA’s Office of Orphan Products Development. If the HUD request is granted, the investigator proceeds with the second step by submitting of a Humanitarian Device Exemption (HDE) application to the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), or the Center for Drug Evaluation and Research (CDER), as applicable. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

Investigators, Sponsors, and Sponsor-Investigators

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. “Sub-investigator” includes any other individual member of that team (21 CFR 321.3). **Sponsor** means a person who takes responsibility for and initiates a clinical investigation (21CFR312.3). The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. **Sponsor-Investigator** means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed (21CFR312.3). The term does not include any person other than an individual. If an academic investigator submits an IND or IDE and is the principal investigator, the investigator is the Sponsor-Investigator and he/she is responsible for regulatory compliance. Academic investigators sometimes equate the term “Sponsor” with the source of the study funding. In fact, there are two types of sponsors: regulatory sponsor and financial sponsor. The regulatory sponsor is the person/entity who initiates and takes responsibility for a clinical investigation. The regulatory sponsor submits the IND or IDE when applicable and is responsible for communications with the FDA. The regulatory sponsor may be a pharmaceutical company, a private or academic organization, or an individual. A financial sponsor may be a company, a department, a non-profit or a government agency. If a pharmaceutical (or device) company is supplying a drug (or device) for an academic study, but will not be submitting the IND or IDE, the company is not the regulatory sponsor. For commercial INDs, the financial and regulatory sponsors are usually the same (i.e. the pharmaceutical or device company).

Issue	Sponsor-Initiated Study	Investigator-Initiated Study
Protocol Author	Sponsor	Investigator
Holder of IND/IDE	Sponsor	Investigator
Injuries and Indemnifications	Sponsor pays (except when caused by the institution or PI-non-compliance, negligence or misconduct).	No indemnification by University; industry will provide indemnification for manufacturing defects and its use of results. No subsequent injury payment is provided.

Issue	Sponsor-Initiated Study	Investigator-Initiated Study
Data	Sponsor owns CRFs and reports provided by sponsor; institution owns medical records and other data.	University owns protocol, documents, research results, data.
Intellectual Property	Sponsor owns patentable inventions conceived and reduced to practice; institution owns everything else.	University owns all inventions and intellectual property.
Funding	Sponsor	Grants; Industry Funding; University; Department

Sponsor-Investigator Responsibilities

Sponsor-Investigator responsibilities under an IND or IDE are covered in 21 CFR Part 312 (for drugs) and 21 CFR Part 812 (for devices). **FDA Guidance:** Search for Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects (https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/whomtocontactaboutorphanproductdevelopment/ucm337104.htm).

Assistance for IND/IDE Preparation

The Research Quality Assurance (RQA) Group is available to assist with IND/IDE preparation, submission and maintenance.

Learn more about RQA (/rqa).

Submit IND/IDE to the FDA

The process and format for submitting an IND application is defined in 21 CFR 312.23, “IND Content and Format.”

The process and format for submitting an IDE application is defined in 21 CFR 812.20, “Investigational Device Exemptions – Application.”

Per Penn State University Policy RP-05, “Research Quality in Human Participant Research,” it is required that the Research Quality Assurance (RQA) group be contacted to provide support for the submission process for IDEs or Study Risk Determinations, and to perform an administrative review of the submission prior to being sent to the FDA.

See Penn State University policy (https://policy.psu.edu/policies/RP05).

See RQA contact details (/rqa).

Preparing Documents

Purpose of Financial Approval Documents

The purpose of these SOPs is to provide guidance to research personnel on how a clinical trial payer Coverage Analysis (CA) and budget negotiation process is under-taken in order to receive institutional and departmental approvals.

See details via the Clinical Trials Office (/cto).

All clinical trials involving human subjects with potentially billable items and services, regardless of the funding source, should have a CA performed. Simply stated, a CA is required for studies that include services billable to insurance (i.e., when it is possible for a charge to be captured in the billing system).

The CA is not needed if a trial uses existing specimens or involves collecting data based on clinical progression. A survey, retrospective or observational study only includes a collection of forms during the patient’s standard of care. Since form collection is not billable to insurance, a CA is not required. The CA is necessary to assist in determining the responsibility of charges in a clinical trial.

What is Coverage Analysis?

A CA is a systematic review of study-related documents to determine the Medicare billing status of both the study and the items/services provided to research participants as part of a clinical research study. The CA process involves the following steps:

- Identifying studies required to undergo CA.
- Creating of the Coverage Analysis Review memo.
- Performing the “qualifying status” of the clinical trial.
- Identifying Routine Costs.
- Constructing the Study Billing Grid.
- Providing the Study Billing Grid as a tool for study team use.

Primary objective: To ensure all costs of a clinical trial are billed to the appropriate payer (sponsor, alternate funding source, institution/department, third-party payer, or participant) Medicare rules are used for various reasons. Foremost, it is not practical to budget on non-Medicare rules since Medicare drives the reimbursement rules in the United States. Medicare incorporates the “most favored nation” clause. This means that if a Medicare patient is enrolled in a clinical research study, the best deal must be given to the Medicare participant. Medicare rules for research coverage are being adopted by commercial payers, with many states already requiring commercial payers to follow rules similar to Medicare. Even pediatric studies go through the CA process since budget negotiations are based off of the coverage analysis results.

Importance of Performing Coverage Analysis

There are multiple benefits to performing a CA. It affords the institution an approach to tease out research-only charges from those items/services that are routine and/or customary care. Used as an asset in preparing a budget, it provides opportunities for increased revenue. Early detection of items/services that are not covered allows for appropriate negotiation. Additionally, we need to know the billing status of all trial procedures in order to perform a proper informed consent process. Participants are entitled to know what their financial responsibility will be during a clinical trial. Finally, it is necessary for compliant research billing processes. Errors in billing Medicare for items/services relative to clinical trials could result in allegations under the False Claims Act. Substantial fines and penalties may result. Loss of trust by sponsors and participants as well as loss of government funding may occur. Since clinical research often takes place in conjunction with the routine clinical care of patients, it is imperative to ensure that billing for both routine and research services/items are handled appropriately and in compliance with all applicable statutory requirements.

Determining Coverage

Determining coverage involves a multi-phased approach.

- Select those trials where a Coverage Analysis necessary.
  - If it is possible for a charge to be captured in the billing system, then a CA is performed.
  - Examples of studies not requiring a CA: existing specimens, data collection on clinical progression.
- Initiate a Coverage Analysis Review memo to document and memorialize the evolution of coverage decisions.

PART 1: IDENTIFY IF A CLINICAL TRIAL "QUALIFIES" FOR MEDICARE COVERAGE

- **Non-device trials:** Consult The Centers for Medicare and Medicaid Services (https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1&ncdver=2&NCAId=210&NcaName=Clinical+Trial+Policy&IsPopup=y&bc=AAAAAAAACAAAAA%3D%3D&) (CMS) for coverage requirements (NCD 310.1: National Coverage Determination for Routine Costs in Clinical Trials).
- **Device trials:** CMS has established regulations for coverage of device trials. Consult the Code of Federal Regulations 42CFR 405.201 – 405.215 and 411.215 and 411.406. Additional information can be found on the Medicare Administrative Contractor's website for our jurisdiction (http://www.novitas-solutions.com/webcenter/portal/MedicareJL/pagebyid?centerWidth=100%25&contentId=00080340&leftWidth=0%25&rightWidth=0%25&showFooter=false&showHeader=false&_adf.ctrl-state=uz38wrf8w_47&_afrLoop=88938623020000#!).

PART 2: PINPOINT ITEMS/SERVICES THAT ARE "ROUTINE COSTS" IN THE STUDY AND POTENTIALLY BILLABLE

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent, or surgery to implant an investigational device);
- Items or services required for the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications (e.g., additional labs to monitor for side effects of the investigational product); and,
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service, in particular for the diagnosis or treatment of complications.

PART 3: REVIEW ALL STATUTES, REGULATIONS, NATIONAL AND LOCAL COVERAGE DETERMINATIONS, MEDICARE MANUALS, AND SPECIALTY SPECIFIC PRACTICE GUIDELINES

Analyzing items/services is solely done for billing purposes, not to judge what the provider should/should not be doing.

FURTHER DETAILS

Medicare/insurance will not cover items and services that are paid for by the sponsor, promised free in the informed consent document, not ordinarily covered by Medicare, and items/services used solely to satisfy data collection or analysis needs. In certain very specific instances CMS can be billed when the study is non-qualifying such as those trials that involve NO changes to medical management or treatment (i.e., observational, registry, or head-to-head). These types of quality trials do not fall under the scope of NCD 310.1. Every effort must take place to ensure that the usual, routine, medically necessary item is not provided based on protocol requirements, but rather would have been provided by the provider even in the absence of study participation.

Claims Processing

Modifiers: A claim that contains an "investigational clinical service" must use the Q0 modifier on the HCFA 1450 form (for facilities) or on the HCFA 1500 form (for physicians). A claim that contains a "routine clinical service" must use the Q1 modifier on the forms. When Q1 is billed in conjunction with the ICD-10, Z00.6 diagnosis code, the Q1 modifier will serve as the provider's attestation that the service meets the Medicare coverage criteria; i.e. was furnished to a beneficiary who is participating in a Medicare qualifying clinical trial and represents routine patient care, including complications associated with qualifying trial participation. **National Clinical Trial (NCT) identifier or Clinicaltrials.gov Number:** CMS requires ClinicalTrials.gov number on the claim when billing "routine costs" during a "qualifying clinical trial." For clinical trial/registry/study claims with dates of service on and after January 1, 2014, this 8-digit clinical trial number must be included or claims will be returned as unprocessable. Study teams are responsible for providing sufficient information to add these identifiers to the claims. **Medicare Advantage Plans (MAPs):** If your study enrolls patients on the Medicare Advantage Plan, you need to be aware of special requirements for copays and claims processing. See the Medicare Managed Care Manual for details (https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326.html?DLPage=1&DLEntries=10&DLFilter=medicare%20managed&DLSort=0&DLSortDir=ascending).

- **Non-Device Trials:** When enrolled in a qualifying clinical trial, Medicare pays for covered services as if in the original, traditional Medicare program (fee-for-service). Providers should split outpatient MAP claims and route the protocol-related "routine care" to traditional Medicare. Additionally, MAPs are responsible for copayments related to services paid under the traditional Medicare rules.
- **Device Trials:** MAPs are responsible for payment of claims related to enrollees' participation in both Category A and B IDE studies that are covered by the MAC with jurisdiction over the MAP plan's service area.
  - The MAP is responsible for payment of routine care items and services in CMS-approved Category A IDE studies.

- The MAP is responsible for payment of routine care items and services, and potentially the Category B device under study in CMS-approved Category B IDE studies.

Clinical Research Coverage Analysis and Billing Guidance

Education materials are available via the College of Medicine Clinical Trials Office's section of this website. Additionally, in-person Clinical Research Skills Workshops are held annually.

Learn more about the Clinical Trials Office (/cto).

Subject Injury and Complications

While the clinical sites typically provide medical treatment to the subjects sustaining injury/complication on the study, who will cover the costs may not always be a clear decision. Industry sponsor, insurance or even self-pay options are considered. For privately sponsored studies that are conducted pursuant to a private sponsor's protocol (industry sponsor), the sponsor of the study is required to pay for the reasonable cost of treating injuries or complications resulting from participation in the study, including injuries or complications resulting from the study material or research procedures performed pursuant to the study protocol, to the extent that injuries/complications were not a result of negligence, willful misconduct or failure to reasonably act on the part of the study personnel. Other costs that are incurred during conduct of the study but not resulting from the subject's participation (i.e., typical for this type of disease or procedure) may be billed to private and government insurers, if consistent with their policies. However, in the case of injuries resulting from the natural progression of a disease or illness, the sponsor would be responsible for any injuries if, and to the extent, the progression resulted from participation in the study. In some cases, determination of whether the complication was directly or indirectly related may not be clear.

Example

> If an investigational medication is administered via an intravenous infusion, and the needle entry site became infected, it does not necessarily mean that this injury is directly related to the investigational drug administration. Other factors need to be considered. For instance, if the standard of care or alternative treatment is an oral medication, then the i.v. infection may be directly attributed to the investigational study drug. However, if the standard of care treatment is also intravenous, then the infection maybe construed as being a consequence of this typical intravenous procedure, and therefore, not directly related to the investigational drug administration.

When the trial is not conducted pursuant to a private industry sponsor protocol, the costs of treating study subjects for injuries or complications resulting from a study material or research procedures will be the responsibility of the subject or the subject's Medicare/private insurance plans. Further guidance is available under "Compensation for Injury" in the HRP-109 – Consent Language Document.

Payments to Research Subjects

It is not uncommon for participants to be paid for their participation in research, especially in the early phases of investigational drug, biologic or device development. Financial remuneration is often used when health benefits to participants are remote or non-existent. Payment to research participants for participation in studies is not considered a benefit, it is a recruitment incentive. However, the payment should appropriate to what is being asked of the participant to do during the study and relative to the potential harm/discomfort of participating in research. The payment should not unduly induce a person to participate.

The Institutional Review Board (IRB) should determine that the risks to participants are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)]. Therefore, the IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that either are coercive or present undue influence [21 CFR 50.20].

The amount and schedule of all payments should be presented to the IRB at the time of initial review. Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire 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 to FDA, providing that such incentive is not coercive. The IRB should 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 set forth in the informed consent document.

For further information, see FDA's Guidance for Institutional Review Boards and Clinical Investigators; Payment to Research Participants Information Sheet.

Penn State University classifies participant payment into two categories: Stipend and Reimbursement. Stipend is payment for participant's (and caregiver's, if applicable) time to participate in research. Stipend can be paid as a flat amount or on a per-hour basis. This type of payment is subject to the U.S. Internal Revenue Service regulations, and may be deemed earned income. Reimbursement is for expenses incurred due to participation in research. Often reimbursement is for travel expenses, thus this category is referred to as "Travel." Travel expenses can be mileage, gas, tolls, airline or train tickets, cab/rideshare fares, and parking. However, Reimbursement can include, but not limited to, hotel expenses related research visits, meals, and supplies/equipment necessary to participate in the research. Reimbursement can be paid as a flat amount or for actual cost upon submission of receipt.

For details, see Penn State's research protections guideline Payments to Human Participants in Research (RPG03) (https://policy.psu.edu/policies/rpg03).

Regulatory Approval: IRB SOPs and Investigator Manual

The Penn State IRB Investigator Manual (HRP-103) provides a wealth of information about the IRB. It is advisable that the investigator consult this document prior to preparing the application. The IRB Investigator Manual is available in the CATS IRB Library. The Penn State IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research studies conducted under the auspices of Penn State University and Penn State Health. The role of the IRB is to review and to make decisions on all research involving human subjects.

TYPES OF REGULATORY REVIEW FOR RESEARCH ACTIVITIES

Submitted research activities may fall into one of the following four regulatory classifications:

- **Not "Human Research:"** Activities must meet the organizational definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Review the IRB "WORKSHEET: Human Research Determination (HRP-310)" for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Research.
- **Exempt:** Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the organization, not the investigator, to determine whether Human Research is exempt from IRB review. Review IRB "WORKSHEET: Exemption Determination (HRP-312)" for reference on the categories of research that may be exempt.
- **Review using the Limited IRB Review Procedure:** Certain categories of exempt Human Research require that the IRB assess some [46.111(a)(7)], but not all, of the 45 CFR 46.111 review criteria. Review IRB "WORKSHEET: Limited IRB Review (HRP-319)" for reference on the categories of research that may be eligible for a limited IRB review.
- **Review Using the Expedited Procedure:** Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review IRB "WORKSHEET: Eligibility for Review Using the Expedited Procedure (HRP-313)" for reference on the categories of research that may be reviewed using the expedited procedure.
- **Review by the Convened IRB:** Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

CRITERIA FOR IRB APPROVAL

In order to evaluate and potentially approve human subjects research, the Penn State IRB must review the protocol and determine that all of the federal requirements for approval, as outlined in 45 CFR 46.111(a)(1-7)(b), are satisfied. The criteria for IRB approval can be found in the "WORKSHEET: Criteria for Approval and Additional Considerations (HRP-314)" for non-exempt Human Research. The worksheet references other checklists that might be relevant. All checklists and worksheets can be found in CATS IRB Library.

WHAT ARE THE DECISIONS THE IRB CAN MAKE WHEN REVIEWING PROPOSED RESEARCH?

The IRB may approve research, require modifications to the research to secure approval, table research, or disapprove research:

- **Approval:** Made when all criteria for approval are met. See "Criteria for IRB Approval" above.
- **Modifications Required to Secure Approval:** Made when IRB members require specific modifications to the research before approval can be finalized.
- **Deferred:** Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- **Tabled:** Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.
- **Disapproval:** Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How to Submit a New Human Research Study to the IRB

The IRB must review and approve all Human Research activities prior to the initiation of any research activities. Create an online application in CATS IRB, and submit it to the IRB along with all required documents. All research submissions must have a protocol attached to the online application in CATS IRB. The purpose of the protocol is to provide the IRB with sufficient information to conduct a substantive review. If a separate sponsor's protocol exists, please submit it in addition to Local Site Plan for Human Subject Research (HRP-595) (see below). The IRB has provided multiple protocol templates, based on the type of research being conducted. Protocol templates can be accessed by navigating to CATS IRB (https://irb.psu.edu) (login required), clicking on the Library link in the left menu and then clicking on the templates tab on that page. The templates are referenced by number and include:

- **HRP-591 – Protocol for Human Subject Research**
  - For social science/non-biomedical/educational research
  - For biomedical research studies not involving the use of a test article (drugs or devices)
- **HRP-592 – Protocol for Human Subject Research with Use of a Test Article(s)**
  - For biomedical research involving the use of a test article (drugs or devices, supplements, alternative medicines and/or chemicals)
  - For biomedical research that falls under the FDA regulations
- **HRP-593 – Protocol for Humanitarian Use Device**
  - For studies involving the use of a Humanitarian Use Device (HUD)
- **HRP-594 – Protocol for Not Human Subjects Research Determination**
  - For activities for which the need for IRB approval or determination is unclear, or
  - For activities requiring written documentation of a not human research determination
- **HRP-595 – Local Site Plan for Human Subjects Research**
  - For multi-center research for which a protocol has been provided by the sponsor or director of the multi-center study. Upload both the sponsor-written protocol and HRP-595 for this type of project
- **HRP-596 – Protocol for Human Subjects Research – Chart review and/or Analysis of Existing Restricted Data Set Study**

    - For studies involving the review of medical records (electronic medical records or paper charts) and/or the analysis of existing restricted data sets *only*. This protocol is *not* for the use of data that does not meet the definition of human subject research. Researchers who are not using human subjects data can complete protocol template HRP-594 – Protocol for Not Human Subjects Research Determination, when necessary.

- **HRP-598 – Research Data Plan Review Form**
    - For all studies reviewed at Penn State College of Medicine, as a supplement to the main protocol document

Use a template protocol as a starting point for drafting a new protocol, and reference the instructions in italic text for information the IRB looks for when reviewing research. Here are some key points to remember when developing a protocol:

- The italicized bullet points included in the gray boxes in the protocol template serve as guidance to investigators when developing a protocol for submission to the IRB. All gray boxes should be left in the final document.
- If the study is a multi-center study, and the sponsor has provided a protocol, upload the sponsor's protocol in CATS IRB and the Local Site Plan for Human Subjects Research (HRP-595).
- When writing a protocol, always keep an electronic copy. You will need to modify this copy when making changes to the protocol, or if the IRB requests changes.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your protocol. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria, as the involvement of subjects in these populations has regulatory implications and requires specific determinations to be made by the IRB:
    - Adults unable to provide legally effective consent
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women
    - Prisoners
    - Neonates of uncertain viability or non-viable neonates
- If you are conducting community-based participatory research, you may contact the Human Research Protection Program (HRPP) for information about:
    - Research studies using a community-based participatory research design
    - Use of community advisory boards
    - Use of subject advocates
    - Partnerships with community-based organizations
    - Appropriate human subject training for community partners engaged in the research

SUPPORTING DOCUMENTS

CATS IRB will prompt the user to upload documents throughout the submission form, including consent forms, protocols, recruitment materials, etc. In addition, any other study-specific documents should be uploaded in the "Local Site Documents" section of the form. Examples of common supporting documents include:

- Data collection instruments, such as:
    - Surveys/questionnaires
    - Interview questions/focus group topics
    - Observation checklists
    - Videos or images that subjects may be asked to view (stimuli)
- Certificates of confidentiality from HHS Agency
- Collaborating approval materials, including:
    - Scientific Review Memo
    - HRP 903 Radiation Review Form – all research involving diagnostic or therapeutic radiation procedures involving ionizing radiation
    - HRP 902 Human Tissue for Research Form – used when a project involves collection of tissue for research
    - Enterprise Information Management (EIM) Design Specification Forms
    - Completed checklist of Department of Energy requirements, if applicable
    - Other IRB approvals
    - Other study-related documents not previously uploaded

INFORMED CONSENT

The IRB has multiple consent templates, based on the type of research being conducted. Consent templates can be accessed by navigating to CATS IRB Library. Use one of the following templates:

- **HRP-580 – HRPP Consent Form Template:** For studies obtaining written informed consent (This is the standard long form consent document discussed in the next section)
- **HRP-581 – HRPP Consent Form Addendum:** To inform current subjects about new information that could affect the subject's willingness to continue in the study
- **HRP-582 – HRPP Consent Form for Emergency Use:** To obtain written informed consent from patients receiving an unapproved drug, biologic or device in an emergency situation
- **HRP-583 – HRPP Consent Short Form:** Use this template for the short form consent documentation
- **HRP-584 – HRPP Consent Guidance for Exempt Research:** For the consent process in research projects that are exempt and involve interactions with research subjects

- **HRP-585 – HRPP Minimal Risk Consent Form Template:** For research in which verbal or implied consent will be obtained and which will not involve the use of protected health information
- **HRP-586 – HRPP Pregnant Partner Consent Form:** For research in which the partner of a subject becomes pregnant during participation in a clinical trial involving investigational drug(s). Note: this document does not have to be submitted with the initial study review but should be used if/when it becomes applicable.

Note that all long form consent documents and all summaries for short form consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. Review the "Long Form of Consent Documentation" section in the IRB's "WORKSHEET: Criteria for Approval (HRP-314)," to ensure that these elements are addressed. The IRB requires that you date the revisions of your consent documents in the header to ensure that you use the most recent version approved by the IRB. The approved version will be watermarked by CATS IRB.

COMMON MISTAKES IN INFORMED CONSENT

- Incomplete and/or inconsistent information
- Language is too complex
- Recruitment and consent process is not well explained
- "De-identified" not a meaningful term by itself
- Standard of care procedures vs. research procedures are not clearly described
- Use of exculpatory language

HELPFUL HINTS: CONSENT VERSUS CLINICAL TRIAL AGREEMENT (CONTRACT)

The Consent Form

- Is not a contract for exchange of services for payment, but an acknowledgement
- It is between Penn State and the participant
- Necessary for regulatory compliance purposes
- Project-specific

The Clinical Trial Agreement (Contract)

- Is a contract for services by PSU/PSH in exchange for payment: required only when we are being paid by a Sponsor to conduct a trial
- It is between PSU/PSH and the Sponsor (the PI and the study subjects are not parties to the contract)
- It is necessary to cover the legal risks between the parties in exchanging services for payment
- May be a template or master and not project-specific

Additional Approvals

APPROVALS REQUIRED PRIOR TO INITIATING RESEARCH

Anatomic Pathology

Research involving the collection of tissues or use of pathologic specimens must receive approval from Anatomic Pathology. Include a copy of the Use of Human Tissue for Research Form with the application materials for research projects that involve any of the following:

- Collection of tissue from surgical or biopsy procedures;
- collection of bone marrow from bone marrow biopsies and/or bone marrow aspirates;
- use of archival pathologic specimens stored in Anatomic Pathology;
- collection of tissue from cadavers; and/or
- collection of placenta specimens.

Any time human tissue is removed for research purposes, the specimen must pass through either the Surgical Pathology Laboratory or Autopsy Suite. Adequate diagnostic tissue will be retained in the laboratory prior to providing specimens for research. Therefore, Pathology is usually able to provide tissues from major surgical excisions but can only rarely provide tissues from small biopsies obtained for diagnostic purposes.

There is a charge per specimen to help defray the technical cost in obtaining research tissues. Call the Department of Pathology at 717-531-8352 (tel:17175318352), for the current charge to use when preparing the budget for a grant. If the investigator is aware that a biopsy or excision of the desired tissue is scheduled, they should complete and submit to the Anatomic Pathology Gross Room (fax to 717-531-0831) a "Research Tissue Request Form" prior to the scheduled date of surgery. This form notifies the Gross Room staff that a specimen is a potential source of research tissue so that the specimen can be handled appropriately for that purpose. A blank copy of this form can be obtained from the Gross Room; this blank form can be photocopied for multiple submissions. Anatomic Pathology approval is required before the IRB will approve the study.

Human Use of Isotope Committee

All research involving radiation procedures (standard of care and/or research-related) must complete the Radiation Review Form and upload it on the Supporting Documents page in the CATS IRB application. If the study involves use of radiation procedures for research purposes, the study must receive approval from the Radiation Safety Committee – Human Use of Isotope Committee (HUIC). HUIC approval is required before the IRB will approve the study.

Clinical Research Center Advisory Committee

Research involving the use of services at the Clinical Research Center (CRC) for any reason, including the use of personnel as back up to the research team or plans to use personnel in the event of an emergency, need to be reviewed by the CRC Advisory Committee. CRC Advisory Committee approval is not required before the IRB will approve the study.

Conflict of Interest Committee (Individual)

Research studies in which a member of the study staff has a financial interest as defined by PSU policies must be reviewed by the Conflict of Interest Review Committee (CIRC-HY). IRB approval will not be granted until the IRB has reviewed the recommended management plan.

Conflict of Interest Committee (Institutional)

Research studies in which an institutional conflict may exist as defined by Penn State policies must be reviewed by the Institutional Conflict of Interest Review Committee. IRB approval will not be granted until the IRB has reviewed the recommended management plan.

Departmental Scientific and Feasibility Review

All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following:

- external peer-review process (e.g., research studies funded by an NIH grant);
- departmental or institute scientific review committees; or
- scientific review by the Clinical Research Center Advisory Committee.

All research studies involving cancer patients, records and/or tissues or cancer prevention studies must be reviewed by the Penn State Cancer Institute Scientific Review Committee.

Institutional Animal Care and Use Committee

Research involving vertebrate animals must receive approval from the Institutional Animal Care and Use Committee. Investigators will need to complete an IACUC application. The IACUC approval is required before IRB approval will be issued.

Data Transfer Agreement Review

Research that involves any transfer of human research data to and/or from any third party requires review by the Office of Research Affairs. This approval is required before IRB approval will be issued. Requests for Data Use Agreements should be submitted via this form (https://pennstatehershey.tfaforms.net/267).

Data Security Plan Ancillary Review

Research in which the data security plan does not meet the requirements of the SOP Addendum – Security and Integrity of Human Research Data require review by the IT Security Group at Penn State Health. Also, research that involves the transfer of PHI or PII to and/or from a third party (exceptions: industry-sponsored, multi-center trials, oncology group studies and studies sharing data with NIH genomic databases) require review by the IT Security Group. The IT Security Group approval is required before IRB approval will be issued.

Medical Education Ancillary Review

Educational research enrolling any of the learner groups at Penn State College of Medicine must be reviewed by the Educational Research Review Committee (ERRC). The ERRC review must be complete before IRB approval will be issued.

IND/IDE Audit Ancillary Review

Research in which a Penn State Health or Penn State College of Medicine researcher holds the IND or IDE or intends to hold the IND or IDE must be reviewed by the Research Quality Assurance Office (RQA) to ensure sponsor-investigator is compliant with FDA sponsor requirements (including GMP when applicable). Also, RQA may be asked to review investigator-written research using marketed drugs in which the researcher does not have an IND and there is no exemption determination from the FDA. The RQA review must be completed before IRB approval will be issued.

Institutional Biosafety Committee

Research involving biohazardous materials (human biological specimens, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy) must receive approval from the Institutional Biosafety Committee. Investigators will need to complete an IBC application. The IBC approval is required before IRB approval will be issued.

BIOLOGICAL USE AUTHORIZATION

Institutional Biosafety Committee (IBC) at The Pennsylvania State University College of Medicine reviews research activities involving biological materials that may pose a risk to human, animal, or environmental health. IBC review and approval is required for research activities involving use of recombinant or synthetic nucleic acids, potential employee exposure to infectious agents, and generation of medical waste outside of clinical (patient care) environments.

Examples of research activities that require IBC review and approval include:

- Unfixed human or non-human primate materials
  - Including use of human blood, tissues and patient samples for research purposes used in clinical trials
  - Primary or established human-derived cell lines
- Biological toxins or carcinogens
- Infectious agents
- Recombinant infectious agents
- Recombinant DNA or synthetic DNA molecules
- Recombinant DNA in animals
- Biohazards in humans
- Biohazards in animals
- Genetically manipulated in animals
- Employee exposure to any of the aforementioned activities or materials, including product manipulation, pack, transporting and shipping

Researchers who plan on conducting research involving use of experimental recombinant or synthetic nucleic acid technologies in human subjects including all human gene transfer research are required to contact the Biosafety Office at the earliest stages of their research plan for advising by emailing biosafetyofficer@pennstatehealth.psu.edu (mailto:biosafetyofficer@pennstatehealth.psu.edu).

Penn State uses the CATS Safety electronic protocol submission system (https://researchsafety.psu.edu/) for all renewal and new submissions.

Approved protocols are valid for 3 years, after which the protocol must be resubmitted with any modifications for a full review by the IBC.

Principal Investigators must submit the protocol through the **CATS Safety system** at researchsafety.psu.edu (https://researchsafety.psu.edu/), prior to submission of 1) the IAF for a grant application to the Office of Research Affairs, 2) animal protocols that involve work with biohazards to the Institutional Animal Care and Use Committee (IACUC), or 3) protocols that involve work with biohazards to the Institutional Review Board (IRB).

In addition, investigators must submit through the CATS safety system when beginning work with a new rDNA source (organism), new sequence (gene or gene region), recipient cell type for rDNA (host), or vector (plasmid or virus). All changes to a protocol approved are to be amended at anytime to update work, add additional clinical trials, training and personnel updates appropriate.

CATS Safety includes an extensive reference section under the CATS Library button. Information includes the appropriate risk group summary, templates, policies , required training matrix and additional biosafety resources.

Activities conducted in clinical environments **that are not used for research purposes,** by employees covered under established health surveillance and infection control plans do not generally require IBC review.

The Principal investigator (PI) is responsible for completing all required training and for ensuring their employees complete required training commensurate with tasks performed. Required trainings include

- CITI Yearly Biosafety Training (https://citi.psu.edu)
- Blood Borne Pathogen (BBP) or Annual infection control training
- Annual Safety Training – Infonet (https://infonet.pennstatehershey.net/web/safety/safety-training)(Penn State Health ePass login required)
- Biological Shipping and Dry Ice training – Infonet (https://infonet.pennstatehershey.net/web/safety/biological-materials-dry-ice-shipping-training) (Penn State Health ePass login required)

Questions regarding the IBC review process or training schedules and requirements should be directed to the Biosafety Officer at biosafetyofficer@pennstatehealth.psu.edu (mailto:biosafetyofficer@pennstatehealth.psu.edu).

Biosafety at Penn State College of Medicine is based on the two primary documents listed below

- The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (https://osp.od.nih.gov/policies/biosafety-and-biosecurity-policy#tab2/) (NIH Guidelines)
- Biosafety in Microbiological and Biomedical Laboratories (https://www.cdc.gov/labs/BMBL.html) (BMBL; sixth edition)
- Penn State Policy RP11 Use of Regulated and Biohazardous Materials in Research and Instruction (https://policy.psu.edu/policies/rp11) (formerly SY24)

STEM CELL RESEARCH OVERSIGHT COMMITTEE

The Institutional Biosafety Committee (IBC) provides administrative support on issues involving stem cell research.

Principle Investigators must add all appropriate information in the CATS safety submission regarding Human Embryonic Stem cell or pluripotent stem cell research.

- Human Embryonic Stem Cell (hESC) and/or Human Induced Pluripotent Stem Cell (hiPSC) Research must also be submitted in the CATS Safety protocol submission system (https://researchsafety.psu.edu/).
- The submission will be reviewed by the Penn State ESCRO committee for formal review and approval.

All research laboratory information is available on the internal informational database, LabManager (https://labmanager.hersheymed.net/). As of Jan. 1, 2023, the LabManager system is being upgraded and only available to the Research Quality Assurance office

TECHNOLOGY EVALUATION PROCESS

Clinical research that requires implementation or use of new applications, systems or devices requires an IT Evaluation prior to the start of the study. This is necessary to determine whether or not the new technology may inadvertently create technical instability or create security risks for the institution. Some examples of research-related technologies that have been evaluated include:

- Mobile devices that are used to gather research data on human subjects
- Software that would be implemented on the Penn State network or that would be used to access the Penn State network
- Clinical devices that require network access or involve data transfer

It is important to note that an IT evaluation is restricted to a review of the technical stability, security and feasibility of technology used at the health system. Approval of applications, systems or devices does not signify a commitment of IT resources, implementation costs or financial approval. Learn more on the IT support section of the Infonet (https://infonet.pennstatehershey.net/web/it/solve-a-problem/technical-support) (internal access only; login required).

Submitting to IRB and Obtaining IRB Approval

Submit Required Documents to IRB

The Human Research Protection Program (HRPP) accepts electronic submissions through CATS IRB, which is accessible at irb.psu.edu (https://irb.psu.edu/). The section of this guidebook on How to Submit a New Human Research Study to the IRB (/research-support/guidebook/#question_howtosubmitanewhumanresearchstudytotheirb) provides additional details regarding the submission of forms and documents through CATS IRB.

To access CATS IRB, you must first have a Penn State Access Account. CATS IRB access is further limited to individuals with authorized CATS IRB user accounts. If, after WebAccess authentication, you receive the message “We are unable to display the requested page due to a problem verifying your authentication information,” you must request access to CATS IRB by emailing irb-orp@psu.edu (mailto:irb-orp@psu.edu).

In addition, all Penn State faculty, staff and students will be required to enroll in and use Microsoft Authenticator (Penn State’s multifactor authentication) as the identify-verification method for accessing secure Penn State resources. For more information, visit Penn State’s Multifactor Authentication (MFA) Setting (https://accounts.psu.edu/mfa) website. The IRB Researcher’s Guide (https://pennstateoffice365.sharepoint.com/:w:/s/VPR-ORP/EZlMs4ykqidJqZHvbjFneQsBJDeZl5puaVQRi76QnNiqcQ), available in the CATS IRB Help Center, provides a step-by-step guide for the study staff for creating and submitting a study, responding to clarification requests, and getting started with modifications, continuing reviews, and new information reports.

Respond to IRB Comments and Obtain IRB Approval

The IRB will provide you with a written decision indicating the IRB's determination.

- **If the IRB has approved the human research:** The human research may commence once all other institutional approvals have been met. IRB approval is active for a limited period of time which is noted in the approval letter.
- **If the IRB requires modifications to secure approval and you accept the modifications:** Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response addressing the specific modification(s) that are in question and submit it to the IRB.
- **If the IRB defers the human research:** The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable and give you an opportunity to respond in writing. In most cases if the IRB's reasons for the deferral are addressed in a modification, the human research can be approved.
- **If the IRB disapproves the human research:** The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to request that the IRB reconsider a decision by submitting a written response to the IRB in the CATS IRB system. If the IRB has disapproved the study or submission, new information that was not previously provided to the IRB must be provided for consideration by the IRB.

File Approvals into Regulatory Study Binder

See the section of this guidebook on documentation maintenance for details.

Submitting Contracts for Approval

Contracts Overview and Submission

The Office of Research Affairs (ORA) at Penn State College of Medicine oversees the proposal submission process and negotiates contractual terms and conditions of awards, all with the goal of promoting, fostering and sustaining excellence in basic and clinical research.

In collaboration with other offices, we strive to provide leadership which promotes the protection of human subject volunteers, the safety of research personnel, the humane treatment of research animals, the stewardship of research funds, the highest standards of ethics, integrity, and objectivity in the research process.

See details about the Office of Research Affairs (/ora).

Clinical Trial Contract Review Process

ORA RECEIPT AND ASSIGNMENT

Once the contract packet is received by the contracts office it is assigned to a contract administrator contract administrator for review, negotiation and final execution. The contract administrator contract administrator will work with the Clinical Trials Office (CTO), and department contact if there are missing elements or delays with negotiations.

ORA INITIAL REVIEW

The contract administrator contract administrator will review the contract for consistency with university policy, state and federal law, using the budget, protocol and internal forms as necessary. The contract administrator may also seek consultation with Risk Management, Legal, IRB, CTO, or other sources as necessary to complete the initial review.

ORA FIRST COMMENTS AND NEGOTIATION TO SPONSOR

The contract administrator will send a marked copy of the agreement to the sponsor. The contract administrator will provide reasonable updates on the agreement to the study team.

END OF NEGOTIATION

Once there is agreement between the contract administrator and the sponsor, the contract administrator and the CTO perform final congruence between the agreement, internal and sponsor budgets and informed consent.

Sponsor/Institutional Execution

Once approved, the contract will be sent for signature, typically starting with the PI signature of acknowledgement to the contract. After the PI signs the contract, the authorized signatories of Penn State College of Medicine and/or Penn State Milton S. Hershey Medical Center or applicable Penn State Health entity sign the agreement on behalf of the institutions. Typically the Sponsor signs last and the agreement is then fully executed. However, the contract will not be awarded until the IRB has approved the project.

Contract Award

After the fully executed agreement is returned to ORA, and the IRB has approved the protocol, the ORA notifies the post-award central finance administrators. The post-award central finance administrators open the extramural account.

Contract Maintenance

After the contract is executed, ORA and CTO will be responsible, upon request from the study team, to negotiate and execute amendments to the project period, budget, or other required changes to the contract as agreed between the sponsor and the institution. Such requests must originate from the study

team, rather than directly from the sponsor.

Study Activation

Establishing a Study Account

For industry-sponsored and federal flow-through studies: Once the study is approved in the Internal Approval Form (IAF) and the Statement of Award (SOA) is issued internally, the IAF information is transmitted over into a form inSIMBA. SIMBAis the accounting and form processing system at Penn State College of Medicine. A notice is sent out to the financial contact for the study and the contact goes into SIMBA to enter information into various fields. The form is sent for final approval by University Park Research accounting. They return the form with a cost center and internal order.

Budgeting Account Funds

The study team uses the cost center and internal order in order to apply expenses to the clinical research study. The financial contact allocates the total statement of award into different general ledgers. The Controller's Office ensures that expenses and income falls within these different categories. These categories are established by the contract and budget with the sponsor. The amounts are negotiated by the pre-award analyst. The income and expense are reconciled by the post-award analyst.

Enter Information in CATS IRB and Hospital Billing

The cost center and internal order is entered into CATS IRB so that the IRB can bill the appropriate study. This information is also entered into the Hospital Finance database so that study related charges can be applied to the account. Investigator effort is applied by adding this information to the salary assignment and allocated based on study activity. Study team effort is applied in a similar fashion depending if they are College of Medicine employees or Penn State Health employees.

Records Necessary for Billing

The Coverage Analysis Review (CAR) memo and billing grid (BGRID) created by the College of Medicine Clinical Trials Office (CTO) will be the sole source of truth for determining the responsible payer for Penn State Health (PSH) billable items and services.

Study Tracking and Analysis for Research (https://research.med.psu.edu/research-support/star/) (STAR) is the sole clinical trial management system to be used for tracking PSH billable items and services for research participant's visits.

The information entered into STAR will allow Patient Financial Services (PFS) to direct charges to the appropriate payer. On a monthly basis, reports are generated by PSH Finance and verified by the study team in order to bill the research services to the study.

See the Clinical Research Monthly Procedure Reports section (http://question_clinicalresearchmonthlyprocedurereports) of this guidebook for details.

Post Information on ClinicalTrials.gov

The ClinicalTrials.gov (https://register.clinicaltrials.gov/) Protocol Registration and Results System (PRS) is a web-based tool used to submit clinical study information to ClinicalTrials.gov. Records submitted through the PRS are available to the public at ClinicalTrials.gov. Contact RQA at clinicaltrials.gov@pennstatehealth.psu.edu (mailto:clinicaltrials.gov@pennstatehealth.psu.edu) for PRS account acquisition and any additional guidance or questions. Also see the User Guide (https://pennstatehealth.ellucid.com/documents/view/11741/active/)(internal access only; login required) to ClinicalTrials.gov Registration at Hershey. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Title VIII of FDAAA, Public Law 110-85, amended the PHS Act by adding new section 402(j), 42 U.S.C. § 282(j). The new provisions require that additional information be submitted to ClinicalTrials.gov established by the National Institutes of Health (NIH)/National Library of Medicine (NLM). This includes expanded information on clinical trials and information regarding the results of clinical trials. This ClinicalTrials.gov registration requirement applies to:

- Any study initiated by an investigator under IND/IDE: The Sponsor-Investigator submits a certification (FDA Form 3674) attesting that the registration data will be submitted as per regulations. Results reporting would also be required for this type of study, due within one year of the study end date. Single-patient, emergency-use INDs do not fall under the referenced section, and therefore are not required to submit certification. Any study not conducted under an IND/IDE but involving drug or device. Most Phase 1 trials are not required to register.
- NIH-funded interventional clinical trials.
- Studies that intend to publish in scientific peer-reviewed journals need to be registered and results entered into ClinicalTrials.gov. Investigators intending to publish clinical studies results in an ICMJE journal (International Committee of Medical Journal Editors) must register before enrollment of first subject. The ICMJE clinical trial registration policy requires prospective registration of all interventional clinical studies, but does not require r results reporting for registered trials. In June 2007, the ICMJE adopted the WHO's definition of clinical trial. Learn more about the definition and ICMJE publication on the ICMJE Clinical Trials Registration FAQs (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/) page and the ICMJE Publishing and Editorial
  Issues: Clinical Trial Registration (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html) page.

POTENTIAL CONSEQUENCES OF NON-COMPLIANCE

- Civil or criminal judicial actions
- Monetary penalties up to $11,383 per day
- Loss of current or future funding

- Rejection for manuscript publication for ICMJE journals

In 2013, the Centers for Medicare and Medicaid Services (CMS) issued a Transmittal requiring new mandatory reporting of the ClinicalTrials.gov clinical trial number (also known as NCT number) on all hospital and professional claims for related items/services. Effective Jan. 1, 2015, it became mandatory to report the clinical trial number on claims for items/services provided in all clinical trials that are qualified for coverage. In order for the NCT number to correctly appear on the claims, the study teams need to provide the NCT number in CATS IRB.

FDA WEBINAR SERIES – OVERVIEW OF CLINICALTRIALS.GOV

In a three-part webinar series, FDA provides a general overview of ClinicalTrials.gov and relevant definitions, laws, and regulations for complying with ClinicalTrials.gov registration and results information submission requirements. Participants will gain an understanding of CDER's role and responsibilities with respect to ClinicalTrials.gov oversight and will hear examples of compliance and enforcement activities CDER has taken to encourage compliance.

ACCESS THE WEBINAR SERIES HERE (HTTPS://WWW.FDA.GOV/DRUGS/NEWS-EVENTS-HUMAN-DRUGS/CLINICALTRIALSGOV-THREE-PART-SERIES)

OTHER RELEVANT LINKS

- NIH Guidance on ClinicalTrials.gov Registration Requirements (https://archives.nih.gov/asites/grants/10-14-2016/grants/guide/notice-files/NOT-OD-16-149.html)
- ClinicalTrials.gov Protocol Registration System (https://prsinfo.clinicaltrials.gov/)

Evaluate Medical Equipment with Clinical Engineering Department

Clinical Engineering is primarily responsible for servicing and supporting technology used in the direct care and treatment of patients. The department also supports some minor clinical laboratory equipment and various devices used in the College of Medicine. The overall scope and responsibility of the Clinical Engineering Department extends into Penn State Health's various off-campus practice sites including, but not limited to, Nyes Road, Elizabethtown, Palmyra, Fishburn Road, Front Street, Middletown, Erford Road, Lancaster, Silver Springs, State College and Wilkes-Barre. FDA-approved equipment used on human patients at Penn State Health requires evaluation and testing by Clinical Engineering. For instance, blood pressure monitors and EKG machines sent by an industry sponsor to support multicenter trials need to be evaluated. Another example would be if a researcher was studying (under an IRB-approved protocol) not-yet-approved ultrasound contrast material provided by a pharmaceutical company, while also using the pharmaceutical-company-owned, commercially available, ultrasound machine, the ultrasound machine would need to be checked by Clinical Engineering. Studies with medical devices that have not yet been FDA approved require an IRB approval, and the evidence of the IRB approval should be provided to Clinical Engineering. For more information, see the Clinical Engineering Infonet section (https://infonet.pennstatehershey.net/web/clinical-engineering) (internal access only; login required) or call 717-531-8410 (tel:17175318410).

INSTITUTIONAL POLICIES AND PROCEDURES

- DE-06SPM, Medical Equipment Management Plan (https://pennstatehealth.ellucid.com/documents/view/896) (login required)
- A-09 HAM, Patient Safety Event Reporting (https://pennstatehealth.ellucid.com/documents/view/825) (login required)
- A-70 HAM, Failure of Medical Product or Device/Equipment (https://pennstatehealth.ellucid.com/documents/view/799) (login required)

File Paperwork into Study Binders

See the Maintain Study Documentation section of this guidebook for details.

Subject Recruitment

Patient Privacy and Security: When Does HIPAA Apply?

When an established patient is being considered for participation in a research study by a clinician involved in the patient's care, the HIPAA rules can be confusing. HIPAA applies when a provider is reviewing a patient's medical record for both treatment and research purposes. In general, under the HIPAA privacy rules, patient's medical information may be accessed for treatment, payment or operational purpose without obtaining prior written authorization. Access to a patient's medical record for any other purposes may require additional steps to be in compliance with privacy laws and rules. This means that when a provider looks at his or her patient's medical record for research purposes, the research-related HIPAA rules apply.

When is Access Considered to be For a Research Purpose?

If a patient's record is reviewed for a treatment purpose (*e.g.*, to view lab results or consult with a referring provider) the research-related rules do not apply. However, once a patient's medical information is viewed for a research-related activity (*e.g.*, to screen for eligibility or review, to review a unique case for possible study, or to collect data) the research-related HIPAA rules apply. For example, if a provider is reviewing a patient's lab report for regular care, this access would be for treatment purposes and the research-related rules would not apply. However, if during this review, the provider notices that the lab value may make them a potential research subject and wants to review the chart further for eligibility; the research-related rules would need to be considered.

What are the Research-Related Privacy Rules that Should be Considered?

In general, before any patient information can be used for a research purpose, the patient must sign and date a study-specific consent form that includes the HIPAA authorization elements or a separate HIPAA authorization form which recites the patient's privacy rights. This is true whether or not the patient is seen by the researcher/physician for medical care. Patient information cannot be used for research-related purposes without a signed patient authorization. There are two limited exceptions: if the IRB has granted a Waiver of Authorization or if the IRB has granted a "Preparatory to Research Authorization." **Important:** Any study data obtained without the proper authorizations cited above may not be used for publication (i.e. journals, abstracts, etc.) or any other purpose and can be subject to notification requirements under state and/or federal laws.

Cohort Discovery Tool and Specific Patient Cohorts

See the section of this guidebook titled “Assessment of Potential Cohort for Feasibility or Recruitment” for details.

HIPAA Waiver of Authorization for Recruitment

A HIPAA Waiver of Authorization can be obtained from the IRB if access to patient data is needed for recruitment purposes.

Describe the need in the “HIPAA Research Authorization and/or Waiver or Alteration of Authorization” section of the protocol template or the protocol site addendum. This section is reviewed by the IRB.

If a partial waiver of authorization for recruitment is granted, access to identifiable patient data to determine if a patient may be a potential research subject is permitted.

IRB approval is confirmed by issuance of the IRB approval memo for the study.

The requirement to obtain authorization may be waived or altered if certain criteria are met. Refer to “CHECKLIST: HIPAA Waiver of Authorization (HRP-441)” in the CATS IRB Library for a list of the criteria.

Authorization may be waived for all, or only some uses of protected health information (PHI) for a particular study. A partial waiver permits the use of PHI for recruitment purposes only, to allow identification and, as appropriate, contact of potential participants to determine their interest in study participation. The requirement to obtain authorization for use of PHI may also be altered or waived for a specific study. An alteration allows a change in certain authorization requirements, while still requiring authorization for the use of PHI. Examples include making an exception to the required language in an authorization or to the requirement to obtain a signed authorization. An alteration must meet the same criteria as a waiver or partial waiver.

To request a partial waiver of authorization for recruitment, you must complete the “HIPAA Research Authorization and/or Waiver or Alteration of Authorization” section in the protocol or protocol site addendum for the study. Appendix A-11 of the IRB Investigator Manual includes a list of informational elements that are considered to be identifiers according to the HIPAA regulations.

For additional information see Penn State Policy RP07 – HIPAA and Research at Penn State University (https://policy.psu.edu/policies/rp07).

Decedent Research

An application for the use of PHI from decedents must be submitted to the HRPP 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. Submit the Request for Research on Decedents' Information Attestation Form (https://forms.office.com/r/7xVcDQznUJ) . If the research will include any identifiers linked to living persons, the project must be approved by the IRB in advance. For more information about the Privacy Rule and decedent research provisions go to: 45 CFR 160.103, paragraph (2)(iv) of the definition of “protected health information.”

Review 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, HIPAA rules allow such a review upon compliance with specified criteria. Prior IRB approval must be obtained before accessing and reviewing PHI to prepare a study. Submit the Review Preparatory to Research Request located under “Forms” for IRB for review and approval.

Disclosure Tracking Database/Quick Disclosure

HIPAA rules require that a record be made of a disclosure of any personally identifiable information that is made without an authorization by the research participant. Therefore, tracking of disclosures will have to be undertaken for all disclosures if a waiver of authorization, an approval for review preparatory to research or an approval for the use of a decedent’s PHI is obtained for purposes of research, and for any disclosures not previously specified in a signed authorization document. For purposes of this policy, “disclosure” means the release, transfer, provision of access to, or divulging in any other manner of PHI to any person, whether or not employed by Penn State Health, Penn State College of Medicine or Penn State University, who is not participating in carrying out the research protocol. The following information about any disclosure must be recorded and made available to the individual who is the subject of the PHI upon request:

- Date of disclosure;
- Name of person/entity that received the PHI;
- Description of what PHI was disclosed;
- Brief statement regarding the purpose of the disclosure.

If a research protocol requires multiple disclosures to the same outside party over a period of time, the following information is adequate:

- For the first disclosure, all of the above must be recorded;
- For subsequent disclosures, tracking can refer to the initial record of disclosure and should include the frequency, periodicity or the number of disclosures that will be made; and
- The date of the last disclosure must be documented.

Large Studies: When tracking is required and involves the disclosure of PHI from more than 50 people, HIPAA rules allow a modified tracking method. In this instance it is unnecessary to maintain a list of the specific persons about whom PHI has been disclosed, but the following information must be available upon the request of any individual whose information may have been included:

- The name and description of all protocols involving 50 or more people for which authorization has been waived, including the purpose of these and criteria for selecting records;
- Brief descriptions of types of PHI disclosed;
- Dates or time periods during which disclosures occurred;
- Contact information (name, address, telephone number) for sponsors and recipient researchers; and
- Statement that a specific individual’s PHI may or may not have been disclosed for a particular protocol or research activity.

In addition, the researcher must also assist in contacting the sponsor and recipient researcher if it is reasonably likely that an individual's PHI was disclosed to them. Tracking information as required by HIPAA rules must be maintained by the principal investigator at least six years, and made available to the Privacy Officer.

Advertise

The IRB must review and approve all materials for human subject recruitment before recruitment efforts begin. An advertisement to recruit subjects is any form of materials whose main purpose is to inform and invite the potential subjects to participate in a research study, including:

- Flyers and handouts
- Letters and emails
- Newspaper or magazine ads
- Posters
- Radio, TV and cable
- Internet postings
- Phone scripts
- Facebook and other social media
- Oral communication

The advertisement should be limited to the information prospective subjects need to determine their eligibility and interest, such as:

- Name and address of the investigator or research facility;
- The condition under study or purpose of the research;
- In summary form, the criteria that will be used to determine eligibility for the study;
- A brief list of participation benefits, if any;
- The time or other commitment required of all subjects;
- The location of the research and the phone number of the person or office to contact for further information.

For FDA-regulated research, the advertisement should not:

- Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation.
- Make claims, either explicitly or implicitly, that the test article is known to be equivalent of superior to any other drug, biologic or device.
- Use terms such as "new treatment," "new medication" or "new drug" without explaining that the test article is investigational.
- Include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
- State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol.
- Promise "free treatment" when the intent is only to say subjects will not be charged for a taking part in the research.
- Include exculpatory language.
- Emphasize the payment or the amount to be paid, by such means as larger or bold type.

Please reference "HRP-315 – Worksheet – Advertisements" in the CATS IRB Library for the IRB's requirements regarding advertisements meant to be seen or heard by subjects. StudyFinder (https://studyfinder.psu.edu) is also available to enhance recruitment efforts. StudyFinder is a web-based recruitment tool for Penn State researchers, managed and sponsored by Penn State Clinical Translational Science Institute (CTSI). It is available to all Penn State researchers actively recruiting participants or volunteers for studies. StudyFinder displays data in a way that is intuitive and user-friendly for the public. Learn more about the process for listing studies on StudyFinder (https://studyfinder.psu.edu/researchers).

Screen Research Participants

Subject screening is the term used to describe research activities performed on participants after obtaining their informed consent. Usually screening activities are performed to ensure subjects are eligible to be enrolled in the study, *i.e.* that the participant meets the inclusion and exclusion criteria for the study. Screening activities include interactions with potential subjects to determine eligibility that would not otherwise have been performed if not for the study. Note that a screen failure is the term used to describe the circumstance in which a subject who has provided consent has subsequently failed to meet eligibility criteria for participation in the study based on screening procedures performed after informed consent was obtained. If some or all of the screening activities will take place before signing the consent form (*i.e.*, by telephone) the screening script has to be approved by the IRB.

Note that a screen failure is the term used to describe the circumstance in which a subject who has provided consent has subsequently failed to meet eligibility criteria for participation in the study based on screening procedures performed after informed consent was obtained. The IRB does consider subjects where informed consent was obtained, but subsequently failed to meet eligibility criteria for participation, enrolled subjects.

Please reference "HRP-585 – HRPP Screening Procedure Consent Form Template" – For studies obtaining consent for procedures that will occur prior to obtaining consent for the main research project.

If the health information is collected (including verbal responses)from a covered entity, by accessing records or stored identifiable biospecimens, and will be recorded or stored, the investigator must obtain an authorization via a HIPAA Authorization Form. This is required from all subjects in research prior to the use of the disclosure of protected health information (PHI) for any research related purposes. Please reference "HRP-587 – HRPP HIPAA Authorization for Research".

Obtain Informed Consent

Please reference the following documents in the CATS IRB Library for the IRB's policies regarding the informed consent process and the written documentation of consent:

- HRP-090 – SOP – Informed Consent Process for Research
- HRP-091 – SOP – Written Documentation of Consent

For additional information on Assent, Telephone/Remote Consent Process and the Short Form Process, see “HRP-103 – Investigator Manual” – This document is available to guide researchers through policies and procedures related to the conduct of Human Research at Penn State. The IRB has multiple consent templates, based on the type of research being conducted. Consent templates can be accessed in the CATS IRB Library. The CATS IRB Library can be accessed by navigating to CATS IRB (http://irb.psu.edu), clicking on the Library link in the left menu, and then clicking on the “Templates” tab.

Submit Copy of Consent to Electronic Medical Record

For all research participants who are also Penn State Health patients:

A copy of the signed informed consent form is to be included in the participant’s electronic medical records for all clinical research (regardless if the study meets the NIH definition of a clinical trial. A copy of the signed consent form is to be sent by inter-office mail to Health Information Services.

Documentation of consent is also to be included in the electronic medical record.

See institutional Clinical Research Standard Operating Procedure 401 for further details, which can be found on the Penn State Health Policy Management Portal (https://pennstatehealth.ellucid.com/) (ePass login required).

Maintain Participant Research Records

See the Maintain Study Documentation section of this guidebook for details.

Scheduling and Registration

Review Scheduling and Registration Training Materials

Schedule training and optimization through CareConnect at CareConnectEducation@pennstatehealth.psu.edu (mailto:CareConnectEducation@pennstatehealth.psu.edu).

Associate the Patient with the Research Study

A patient should be associated with the study after signing the Informed Consent utilizing the Alerts Tab in PowerChart. The initial signed Consent Form and all Consent revisions (if a patient was re-consented), must be uploaded into the EMR for each patent enrolled in the study.

Health Information Services is responsible for the consent upload.

The signed paper copies may be sent to HIS by interoffice mail (see the “Submit Copy of Consent to Electronic Medical Record” section of this guidebook for details).

A member of the clinical trial research team is responsible for entering human subject participant information into the PowerChart “Alerts Tab” for all ongoing investigational drug or device clinical trials.

See details via the Clinical Trials Office (/cto).

Creating Research Order Sets

All new order sets or revisions to existing order sets in Connected must now be submitted by completing a form.

The form is available via the Clinical Trials Office (/cto).

Clinical Research Monthly Procedure Reports

The study coordinator, or another designated study team member, will receive a monthly report from Penn State Health (PSH) Finance summarizing the charges appearing in the billing system as research related charges for a designated study, including the amount being billed to the College of Medicine.

Study teams should expect to see all charges within two months of the items and services being rendered. If charges have not been listed, the study team is responsible for contacting PSH Finance to investigate further. If STAR entries are incorrect or not completed in a timely manner, misbilling can occur.

CHARGE REPORTS ARE CORRECT

Once the review of the report is complete, sign the report where indicated and return to the attention of PSH Finance by the due date. Send a copy to the appropriate central Financial Analyst as well. If clinical research monthly procedure reports are not signed and returned to PSH Finance within three months, the research charges will be deemed correct and billed to the respective study budget. PSH Finance will not adjust any charges after this time.

CHARGE REPORTS NEED TO REVISION

If there are services listed on the report that are not research related or not priced correctly, the study team member must notify PSH Finance immediately to have them corrected. Once the report is corrected, a revised copy will be sent for signature.

REVISE/AMEND PREVIOUS CHARGE REPORTS

Any changes requested to previously billed charges will only be made within three months of the original charge(s) in question. Changes after three months is at the sole discretion of PSH Finance.

FURTHER INFORMATION

See policy “Use of Clinical Research Funds” (PSHAM F-17) (https://pennstatehealth.ellucid.com/documents/view/315) for further details, which can be found on the Penn State Health Policy Manager (ePass login required).

Investigational Drug Pharmacy (IDS)

Introduction to IDS

An investigational drug is defined as a new drug or biological that is used in a clinical investigation and which has not been approved for general use by the U.S. Food and Drug Administration. It may also be a drug which is FDA-approved and is being used in a clinical investigation, possibly outside the use of the FDA-approved labeling. The FDA requires that the investigator or designee establish a record of receipt, storage, use/dispensation, and disposition of investigational drugs. At Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine, all investigational drugs are handled by the Investigational Drug Service (IDS) Pharmacy, a division of the Department of Pharmacy. IDS manages the receipt, storage, dispensation, return and disposal of study drugs in accordance with Good Clinical Practice Guidelines, the study protocol requirements, and all applicable rules and regulations.

IDS Contact Information

Shipping address: Investigational Drug Service Pharmacy Penn State Health Milton S. Hershey Medical Center 500 University Dr. Room PG200, MC CH79 Hershey, PA 17033 **Phone:** 717-531-4976 (tel:17175314976) **Fax:** 717-531-5705 **Email:** hmcrxids@pennstatehealth.psu.edu (mailto:hmcrxids@pennstatehealth.psu.edu)

Overview of Investigational Drug Management Process

CONTACT IDS

- Site selection visit
- Budget estimate
- PI-initiated study consult

IRB APPLICATION

SETUP STUDY

- Site initiation visit
- Create order template
- Order/receive study drug
- Build computer codes
- Randomization
- Drug compounding
- Staff training

ACTIVATE STUDY

- Order processing
- Drug preparation
- Drug accountability
- Monitor visit(s)

CLOSE STUDY

- Drug return/destruction
- Close-out visit
- Study archive

Receipt of Investigational Drugs

The principal investigator instructs the sponsor to ship the study medication directly to the IDS Pharmacy. Upon receipt of study shipments, an IDS staff member will inventory/check the shipment using the shipping invoice, notating lot number, expiration date, breakage, storage condition, and total quantities. The shipping invoice will be signed and dated. The shipment will be recorded on the drug accountability log specific for that study. If applicable, the shipment will be activated in the Interactive Voice/Web Response system and/or the packing list will be faxed to the sponsor. The shipping invoice will be filed in the shipping file for that specific study. The study medication will be placed into the appropriate storage conditions, as designated by the sponsor.

Storage of Investigational Drugs

Investigational drugs will be stored separately from other hospital medications, and will be marked (at a minimum) with the drug name, study short name, and IRB number. Dedicated investigational drug refrigerators and freezers will be utilized to store refrigerated and frozen investigational drugs. The outlets for the refrigerators and freezers are connected to the back-up generator. Minimum/maximum temperature logs or continuous electronic temperature monitoring logs for all storage conditions will be maintained daily. IDS will only utilize the institution’s approved, calibrated temperature monitoring device/system. Sponsor provided temperature monitoring devices will not be utilized to record temperature for specific studies during storage on site.

Investigational Drug Inventory

A perpetual inventory will be maintained for every study, to include drug receipt, dispensation, return, and destruction. The IDS pharmacy will not maintain drug accountability records for standard of care medications that are not supplied for the study. The inventory will be audited by the IDS Clinical Trials Assistant or designee. An appropriate minimum inventory will be maintained, based upon the rate of patient enrollment. At the end of a study, the perpetual inventory will be “zeroed out” and the drug will be disposed of/mailed back to the sponsor upon sponsor approval (refer to section 13.3 for additional information pertaining to study closure).

Dispensing Investigational Drugs

The pharmacy may dispense study drugs supplied for clinical trials only upon the receipt of a written physician order sheet or outpatient prescription signed by a physician-investigator authorized in the state of Pennsylvania to prescribe study drugs, as included on his/her clinical practice agreement. The ordering physician must be included on the study’s 1572 form as an investigator or co-investigator. In order for the drug to be dispensed, the prescription/physician order must contain ALL information required by state and federal law as well as the following information:

- Patient’s name
- Patient’s allergies
- Medical record number
- Protocol name
- IRB and/or PSHCI number
- Drug information
    - Name
    - Dose
    - Route
    - Schedule of administration
    - Quantity to dispense
- Physician name
- Physician signature

The initial order must also contain verification that the study participant signed the informed consent document by including one of the following:

- First page and signed Signature Page of the consent form
- Documentation on physician’s order sheet of date and time that the informed consent was signed

The drug will be prepared and dispensed per protocol specifications and established pharmacy policies. Dispensed study medication will be labeled with the Pharmacy Department’s computer-generated label, which conforms to state and federal law. The sponsor’s required labeling will be attached to the dispensed product in addition to the pharmacy label. No parts of the sponsor’s label will be obliterated by the pharmacy label. All study medications will be labeled with the caution, “For Investigational Use Only.” The administration of investigational drugs while in an Ambulatory Care Center, Infusion Room, or while admitted to the hospital, is the responsibility of the principal and co-investigators identified in the study protocol. An investigational medication may only be administered according to protocol and institutional specifications.

IDS and Monitoring Visits

The IDS Pharmacy staff will meet with study monitors/auditors in order to assure protocol compliance/adherence. The study coordinator or study monitor must schedule the monitoring visit with the IDS Pharmacy at least two weeks in advance. The IDS Pharmacy will schedule a maximum of three monitor visits or a total of five “monitoring hours” per day.

Requests to Unblind a Patient's Study Treatment

The investigator must provide the pharmacy with written permission to unblind a subject’s treatment. This may be in the form of a written order or an email. The IDS pharmacy will unblind the patient and place a copy of the written correspondence in the study file/binder.

IDS Policies

IDS Pharmacy Policies may be viewed on the Infonet (https://pennstatehealth.ellucid.com/manuals/binder/123) (internal access only; login required). The list below includes some of the available IDS policies:

- Ordering and Dispensing Investigational Drugs
- Temperature Monitoring of Investigational Drugs in the Pharmacy
- Essential Document Handling and Retention
- Cost Estimate
- Destruction of Investigational Drugs
- Dispensing Investigational Drugs to a Home Health Care Agency
- Drug Accountability, Inventory Management and Returns
- Handling Investigational Biosafety Level 2 Products BSL2
- Monitors and Auditors
- NCI-Registered Investigators to Prescribe CTEP-Supplied Agents
- Pharmacy Staff Training for Investigational Drug Studies
- Storage of Investigational Biosafety Level 2 BSL2
- Transport of Investigational Drugs by Penn State Health Milton S. Hershey Medical Center Pharmacy

- Use of Investigational Drugs

Clinical Trial Maintenance

Reporting Modifications to the IRB

It is advisable that you **consult the Penn State University IRB Investigator Manual** (HRP-103) in the CATS IRB Library for details regarding changes to the study team or Other parts of the study and protocol exceptions prior to preparing your application. You 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 subjects. Refer to the Expanded Access Submissions (https://www.research.psu.edu/irb/expandedaccess) page on the HRPP website for instructions. In the case of changes implemented to eliminate immediate hazards to the subjects, the emergency protocol changes must be reported to the IRB using a Reportable New Information submission within 5 business days. See New Information that Needs to be Reported to the IRB During the Course of the Study.

To request modifications to an approved study, click “Create Modification / CR” in the CATS IRB system, answer the questions on each screen, attach all requested supporting documents and click the “Submit” activity in the workspace to send it to the IRB Office for review. When revising previously approved documents, such as protocols, consent forms, recruitment materials, etc., use a tracked changes feature and a version date to denote all revisions. Maintain electronic copies of all documents submitted to the IRB in case revisions are required. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

A protocol exception is a one-time, intentional action or process that departs from the IRB-approved study protocol, intended for one occurrence or applied to a single individual. This action must be approved prior to its implementation by the following:

- the sponsor or funding agency
- the IRB
- the FDA (if applicable)

An example of an exception may include: the potential enrollment, following approval of the sponsor, of a subject who fails to meet all of the protocol eligibility criteria. To request a protocol exception for an approved study, click “Create Modification / CR” in the CATS IRB system. In the modification summary section, provide the following information about the protocol exception:

- Description of the protocol exception, including a reference (page number or section) in the IRB-approved protocol that is being altered
- Justification for the protocol exception
- Discussion of the impact on the risks and/or benefits
- Discussion of the impact on the overall safety of the subject
- Discussion of the impact on the overall validity of the study
- Indication if the exception will be discussed with the subject and the rationale for this decision
- Indication of when the approval of the protocol exception is needed

If applicable, attach the sponsor’s and/or FDA’s approval of the protocol exception on the Local Site Documents page under question 3 Other attachments in CATS IRB. Click the “Submit” activity in the workspace to send it to the IRB Office for review.

Submit Continuing Review Progress Reports and Administrative Reviews to the IRB

For any study that requires continuing review, a continuing review form must be submitted prior to the expiration date of IRB approval. Where continuing review is required, the approval letter will indicate this. The IRB sends out multiple courtesy notices starting at approximately 90 days prior to the approval expiration date. It is the Principal Investigator’s responsibility to ensure the required information is submitted by the administrative due date in order to receive renewed approval prior to the expiration date. If the continuing review application is not received **at least 6 weeks prior** to expiration, the IRB may not be able to conduct a timely review, which may result in a lapse of IRB approval. Repeated instances of late submissions that result in a lapse of approval may be considered serious and/or continuing non-compliance. It is advisable that you consult the Penn State University IRB Investigator Manual (HRP-103) in the CATS IRB Library prior to preparing the continuing review form. To submit a continuing review, click “Create Modification /CR/Admin Review” in the CATS IRB system, answer the questions on each screen, attach all required supporting documents and click the “Submit” activity in the workspace to send it to the IRB Office for review. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the continuing review involves a minor modification to previously approved research (e.g., adding a study team member or correcting a typographical error on a consent document), choose ‘Modification and Continuing Review’ on the first screen and submit those modifications as part of the continuing review. IMPORTANT: If the requested changes are more than minor changes, you must complete and submit the ‘Continuing Review’ submission and a separate ‘Modification’ submission. Also note that combined Modification and Continuing Review submissions must be processed and reviewed together (i.e., a minor modification will be approved with the continuing review, not before). If you expect one submission to be reviewed and approved before the other, then submit separate submissions (one modification, and a separate continuing review).

If IRB approval lapses, all Human Research procedures related to the protocol under review must cease including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures without IRB approval is a violation of institutional policy and in some cases a violation of federal regulations. If current subjects will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current subjects. If the PI believes that current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the HRPP at irb-orp@psu.edu (mailto:irb-orp@psu.edu) and provide a written list of the currently enrolled subjects and why they will be harmed by stopping procedures. Remember that research data cannot be collected when a study has lapsed. In addition, the HRPP will administratively close any study that is in a lapsed state for more than 45 days. Once closed, these studies cannot be re-opened and a new submission would have to be completed to continue any human research activities.

Annual Notices

Certain studies approved on or after Jan. 21, 2019, do not require continuing review; however, investigators will receive an annual notice in the study submission as a reminder that the principal investigator remains responsible to comply with all Investigator Responsibilities outlined in this manual until the principal investigator requests that the study is closed through a continuing review (CR) submission.

Principal Investigators responsibilities include, but are not limited to:

- Submitting any modifications that require approval (See Section: *Regulatory Classifications of Research (Not Human, Exempt, Expedited, Full/Convened IRB and Exempt Modifications*))
- Submitting any reports of new information to the IRB (See Section: *Reportable New Information (RNI)–Information to be Reported to the IRB*)
- Submitting a continuing review (CR) to close the study when the research is complete (See Section: *Study Closure Information)*

Reporting New Information to the FDA and the Sponsor

REPORTING UNDER IND (PROTOCOL AMENDMENTS)

You need to submit an IND Protocol Amendment if you have either of the following changes during the course of your study:

- New protocol
- Change in protocol
- New investigator (new site)

The study may begin after you obtain IRB approval based on the new or amended protocol and after the FDA receives the amendment. FDA does not issue “permissions” or “approvals” for protocol amendments, your changes are effective immediately upon the receipt of your amendment by the FDA. The IRB may request documentation of FDA review of amendments and may hold approval until documentation is received from the FDA. In these cases, the PI must request that the FDA provide documentation that the research may continue. For changes in the **protocol**, the IND Protocol Amendment consists of:

- Cover Letter identifying the submission as “Protocol Amendment: Change in Protocol” or “Protocol Amendment: New Protocol”
- Form 1571 – Check an appropriate box under Paragraph 11, “Protocol Amendments”
- A document outlining the differences between the new protocol and the original protocol

For changes in the **investigators**, the IND Protocol Amendment consists of:

- Cover letter identifying the submission as “Protocol Amendment: New Investigator”
- Form 1571 – Check an appropriate box under Paragraph 11, “Protocol Amendments”
- Form 1572 for the new investigator

If there are **manufacturing** or other changes, such as:

- Changes in chemistry, manufacturing and control,
- Changes in pharmacology/toxicology (new findings affecting safety and efficacy), or
- Decision to discontinue a clinical study,

the manufacturer (in many cases, industry sponsor) will notify you. Your responsibility is to notify the IRB and make a decision as to whether to proceed with your trial.

REPORTING UNDER IDE (IDE SUPPLEMENTS)

Any changes in the Investigational Plan should be approved by the FDA and, when appropriate, IRB, prior to implementing any change to a previously accepted Investigational Plan. The following types of protocol changes would require an approved IDE Supplement, because they are likely to have a significant effect on the scientific soundness of the trial design and/ or validity of the data resulting from the trial.

- Change in indication
- Change in type or nature of study control
- Change in primary endpoint
- Change in method of statistical evaluation
- Early termination of the study (except for reasons related to patient safety)
- Change in the number of investigational sites
- Change in the number of study subjects

However, if the modifications meet certain criteria, the sponsor of an IDE may modify the device and/or clinical protocol without prior FDA approval. The sponsor still needs to provide notice to FDA within five working days of making the change. These notices must be identified as a “notice of IDE change.”

- **Emergency use:** If PI deviates from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such deviations should be reported to the IRB promptly after its occurrence, and to the FDA within five working days after the sponsor becomes aware of it.
- **Certain changes to the device:** Advance IRB notification is not required if the changes do not constitute a significant change in design or basic operation and are made in response to information gathered during the course of an investigation. Examples include: creditable data generated under the device control procedures (21 CFR Sec. 820.30), preclinical/animal testing, peer reviewed published literature, and clinical information gathered during a clinical trial or marketing.
- **Certain clinical protocol changes:** When they do not affect (i) the validity of the data or information resulting from the completion of the approved protocol, or the relationship of the likely patient risk to benefit ratio relied upon to approve the protocol; (ii) the scientific soundness of the investigational plan; or (iii) the rights, safety, or welfare of human subjects involved in the investigation.
- **If changes will be submitted in the annual report:** A sponsor may make minor changes to an Investigational Plan without prior FDA approval; provided that the respective changes are reported in the annual progress report for the IDE (see Annual Reports).

For details, see the RQA section of the Infonet (https://infonet.pennstatehershey.net/web/research-quality-assurance) (internal access only; login required).

Reporting Adverse Events to the FDA and Sponsor

Adverse Event (AE): An adverse event is an undesirable and unintended event occurring as a result of therapy or other intervention (e.g., headache following spinal tap or intestinal bleeding associated with aspirin therapy). It also includes any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research. **Serious Adverse Event (SAE):** Events are classified as serious if they meet any of the following criteria:

- Results in death or any life threatening event that places the subject at immediate risk of death from the event as it occurred.
- Any event that requires or prolongs in-patient hospitalization.
- Any event that results in persistent or significant disability/incapacity.
- Any congenital anomaly/birth defect diagnosed in a child of a subject who participated in the study and received study drug.
- Other medically important events that in the opinion of the investigator may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Unanticipated AE: Any adverse experience, the frequency or severity of which is not consistent with the current consent form or investigator brochure. **Unanticipated Problem Involving Risk to Participants or Others:** Any unanticipated event involving any aspect of a research study involving anyone (participants, research staff, or others not directly involved in the research) that increases the risk to the person involved. See DHHS Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html) (includes flowcharts and diagrams)

Reporting SAEs to the Sponsor

Once an adverse event becomes serious, the site should inform the Sponsor by submitting an SAE report. Typically, the Sponsor will provide the report form to use and inform the study investigator/coordinator where and how (i.e. email, fax, etc.) to send the report. An SAE report should be submitted to the Sponsor no later than 24 hours after the site becomes aware of the event. As the site gains more information (i.e. admission records, hospital discharge summaries) updated SAE reports with the new information should be submitted to the Sponsor. In this case the Sponsor (Industry/cooperative group) holds the IND and is therefore responsible for deciding whether the SAE should be reported to the FDA.

Reporting SAEs to the FDA (for investigator-initiated studies under IND or IDE)

IND SAFETY REPORTS

In cases where the PI is both the Investigator and the Sponsor, the PI assumes the responsibility of reporting certain SAEs to the FDA. Once it is determined that an SAE must go to the FDA an IND Safety Report is prepared (usually the PI, in association with the medical monitor, will determine whether an IND Safety Report needs to be prepared). An IND Safety Report is an expedited, written notification to the FDA of an adverse experience associated with the use of a study drug that is both serious and unexpected.

When to file:

- For any unexpected fatal or life threatening SAE associated with the use of the drug, the IND Sponsor-Investigator notifies the FDA of the SAE by telephone or fax as soon as possible, but no later than seven calendar days after initial receipt of the SAE. The investigator follows with the written report no later than 15 days after the occurrence.
- For serious and unexpected, but non-fatal adverse events, file as soon as possible and no later than 15 days after initial receipt of the SAE.

For more on filing requirements and follow-up, see IND Application Reporting: Safety Reports (https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports).

IDE SAFETY REPORTS

An unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. If the Investigator is a Sponsor-Investigator, he/she will notify the FDA and all participating investigators in a written IDE safety report of any unanticipated adverse device effects. The report is also provided to the device manufacturer and to the reviewing IRB as soon as possible, but no later than 10 working days after the Investigator first learns of the effect. Thereafter the sponsor (or Sponsor-Investigator) shall submit such additional reports concerning the effect as FDA requests. See IDE report details on the FDA website (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046717.htm).

Reporting Protocol Deviations to the Sponsor

In many cases Sponsors will specify at the beginning of the study how they would like to handle protocol deviations. Minor deviations (as described elsewhere in this Guidebook) are usually recorded in the case report forms and tabulated by site at the end of the study. Most Sponsors do not require that minor deviations be reported in any immediate fashion. For major deviations the site often reports to the Sponsor are required. In the case where a site needs a deviation in order to enroll a patient that is not otherwise eligible per the protocol inclusion/exclusion criteria, a Sponsor will request that a planned protocol deviation be filed requesting permission from the Sponsor for the site to enroll the patient. Sponsors will respond to this request in writing and this form along with documentation of all communication between the site and Sponsor should be kept in the patient's source documentation. IRB approval is also needed for these one-time protocol exceptions.

Reporting Protocol Deviations to the FDA (for Investigator-Initiated Studies under IND and IDE)

REPORTING PROTOCOL DEVIATIONS UNDER IND

(Information adapted from www.firstclinical.com (http://www.firstclinical.com)) FDA's regulations have numerous references to "changes" or "amendments" to study protocols. For example, 21 CFR 312.30 addresses the responsibility of sponsors to submit amendments to their IND(s) to ensure that clinical investigations are conducted according to protocols included in the application. 21 CFR 312.30(b) specifically discusses changes in a protocol, and provides several examples of changes that would require sponsors to submit protocol amendments to the IND. However, the FDA

regulations do not provide specific guidance on deviation reporting. A protocol deviation directed at eliminating an apparent immediate hazard to a research subject or group of subjects may be implemented immediately provided that the reviewing IRB is so notified. The respective protocol deviation should be addressed in the next Annual Report to the IND application. If the protocol deviation will be incorporated as a permanent change (i.e., revision) to the protocol, a respective Protocol Amendment must be submitted prospectively to the IND application/FDA and the revision to the protocol must be approved prospectively by the responsible IRB.

REPORTING PROTOCOL DEVIATIONS UNDER IDE

FDA device regulations at 21 CFR 812.150(a)(4) discuss protocol deviations under IDE regulations. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB should be made aware in accordance with 812.35(a).

Submit Annual Reports to the FDA

ANNUAL REPORTS TO CDER

For clinical trials being conducted under an IND, FDA requires an annual report from the Sponsor or Sponsor-Investigator. The annual report is due within 60 days of the anniversary date that the IND went effect (i.e., the date that the FDA permitted the study to begin). Required content is listed in 21 CFR 312.33. See the RQA Infonet section for details (https://infonet.pennstatehershey.net/web/research-quality-assurance) (internal access only; login required).

ANNUAL REPORTS TO CDRH

For clinical trials being conducted under an IDE, FDA requires Sponsors to submit progress reports, at regular intervals, and at least yearly. Reports must be submitted to all reviewing IRBs and in the case of significant risk devices the sponsor must also submit the progress report to FDA (21 CFR 812.150). See the RQA Infonet section for details (https://infonet.pennstatehershey.net/web/research-quality-assurance) (internal access only; login required).

Maintain Study Documentation

“Essential documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.” (ICH Guideline E6) There are many ways to organize essential documents, and there is no gold standard for how to do this. For example, the ICH GCP E6 guideline recommends that the documents be grouped according to the stage of the trial, i.e. documents relevant to the trial before it commences, documents relevant to the trial during the conduct of the trial, and those documents relevant to the trial after completion or termination of the trial. See specific information here (https://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial). The most important thing is that the documentation is organized and that all of the necessary documents are present. This section of the Guidebook provides examples of a potential system to organize essential documents. Essential documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial. These documents are also the ones which are usually audited by the independent audits and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected. Another way to organize the essential documents into study binders is by the content of the binder. For example, many sites have a “source document binder,” a “case report form binder,” a “financial binder” and a “regulatory binder.”

Regulatory Binder

Industry sponsors may provide investigators with a regulatory binder to be used to maintain the essential documents for the trial.

Investigators who are conducting investigator initiated trials are encouraged to use either of the two resources available to maintain essential documents.

These two resources are:

- The Virtual Regulatory Binder inserts for regulatory documents maintained in paper format.
- REDCap eRegulatory Binder for electronic storage and organization of regulatory documentation.

The binder tab inserts and instructions, as well as additional information regarding access and utilization of the REDCap eRegulatory Binder, can be found via the Clinical Trials Office (/cto).

The following list represents the required essential documents that must be filed in the regulatory binder. All essential documents must be available for audit/inspection by the sponsor and regulatory authorities.

The Virtual Regulatory Binder adapted from Partners Healthcare provides all essential tabs and information about what needs to go under each tab.

Tab	Documents	References to Regulations
Protocol	• Current protocol and all previously approved versions • When applicable, a copy of the fully executed protocol signature page for original protocol and all approved versions	ICH GCP E6 Sections 8.2.2 and 8.3.2
CVs & Licensure	• Signed and dated CVs for all study staff • Valid medical licenses/professional certifications for all study staff	ICH GCP E6 Sections 4.1.1, 8.2.10, 8.3.5

Tab	Documents	References to Regulations
Logs	• Pre-Screening Log: Captures subjects who have been pre-screened to determine initial eligibility for enrollment. • Enrollment Log: Captures all subjects who sign a consent form. • Delegation of Authority/Delegation of Responsibility Log: Documents the study-related procedures delegated to staff. The PI should initial, sign and date this list, and update it as new staff or study procedures are added to the protocol; see below this table for details • Training Log: Documents training of all study staff on protocol-related procedures; see below this table for details • Adverse Event Tracking Log: Tracks and ensures timely reporting of all applicable adverse events to the IRB; often done electronically • Minor Deviation/Violation Tracking Log: Provides a record of all minor deviations from the approved protocol and facilitates reporting at continuing review; often done electronically • Tissues and/or Blood Sample Log: Tracks tissue and/or blood samples collected during research	ICH GCP E6 Sections 8.3.20, 8.3.25
IRB	• Signed and dated submissions ◦ Application ◦ Continuing review(s) ◦ Amendments ◦ Adverse events ◦ Violations/deviations ◦ Closeout information • Approval letters and/or notification of IRB decisions • Investigator response(s) to IRB notification (if applicable) • Approved recruitment materials • Approved educational materials/additional study information distributed to subjects (e.g., subject diary) • Memo regarding FWA, IRB registration • Copy of IRB membership roster • Any additional correspondence relating to the study, such as emails	ICH GCP E6 Sections 8.2.7, 8.2.8; Code of Federal Regulations 45 CRF 46, 21 CRF 50, 21 CRF 56
Consent/ Assent Forms	• Current IRB-approved consent and/or assent form version(s) with the IRB approval stamp	Code of Federal Regulations 45 CFR 46, 21 CFR 50, 21 CFR 56; ICH GCP E6 Sections 8.2.3, 8.2.7, 8.3.2, 8.3.12
Financial Disclosure	• Signed and dated FDA Financial Disclosures for all clinical investigators listed on the form FDA 1572 (drug) or IRB application (device)	Code of Federal Regulations 21 CRF 54
Laboratory Documents	• Current lab certification (e.g., CLIA, CAP) • Normal lab/reference values	ICH GCP E6 Sections 8.2.11, 8.3.6
Drug/Device Accountability	• Drug/device shipment and receipt records • Drug/device accountability log • Most recent version of investigator's brochure or device manual	ICH GCP E6 Sections 8.2.14, 8.2.15
Data Collection	• Blank set of CRFs, data collection sheets, and IRB-approved study questionnaires • If data are being captured electronically a copy of the eCRF completion guidelines could be filed here	21CRF 312; ICH GCP E6 Sections 8.3.14, 8.3.15, 4.9.3
DSMB (if applicable)	• Copy of all Data and Safety Monitoring Board (DSMB) reports • Additional correspondences with DSMB (e.g., meeting minutes, information provided to the DSMB, emails)	Guidance for Clinical Trial Sponsors-Establishment and Operation of Clinical Trial Data Monitoring Committees, Section 4.4.3.2
Correspondence	• All relevant communications, other than site visits, to document any agreement or significant discussions regarding trial or administration, protocol violations, trial conduct, adverse event reporting, etc. • Includes communications to and from the Sponsor and/or the study team • Communications about a specific subject should be filed with source documents for that subject	ICH GCP E6 Sections 8.3.11

Tab	Documents	References to Regulations
Monitoring	• Monitoring Log: Documents any form of study oversight/monitoring. Both the monitor and clinical research coordinator should sign the log. • Pre-study Visit Report, Site Initiation Visit Reports, Monitoring Visit Reports, Close-Out visit reports or follow up letters if visit reports are not provided.	ICH GCP E6 Sections 8.2.19, 8.2.20, 8.3.10, 8.4.5
Subject Identification Code List	• This is a document containing a unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.	ICH GCP E6 Sections 1.58, 8.3.21, 8.4.3
Final Study Report	• Final report by the Investigator to the IRB, and where applicable, to the regulatory authorities to document completion of the trial.	ICH GCP E6 Section 8.4.8

DELEGATION OF AUTHORITY/RESPONSIBILITIES LOG

It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator).

However, the Principal Investigator (PI) is ultimately responsible for the conduct of the study.

When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. A Delegation of Authority log should be created documenting delegated tasks to delegated individuals. The same applies to staff/contract organizations no in direct employ of the investigator.

Example:

Title of the study

Name	Title	Task(s)	Start Date	End Date	Signature of Delegate
John Smith	CRC	Consent; Delivery of investigational drug from IDS to clinic	1/1/2020	1/31/2020	(signature here)

Below the log, the PI should sign and date.

TRAINING LOG

The investigator has to assure that the staff has appropriate education, training and experience to perform delegated tasks.

The training log should also document that individuals have been trained on protocol-specific topics relevant to their job responsibilities. This training is documented in the training log.

The investigator should develop a plan for the supervision and oversight of the clinical trial at the site. Supervision and oversight should be provided even for individuals who are highly qualified and experienced.

Such a plan is outlined in the FDA Guidance on Investigator Responsibilities and may include routine meetings, procedures for reviewing staff performance, procedures for correction of protocol deviations, and procedures for ensuring quality control.

Source Document Binder

Per ICH GCP guideline E6 section 5.1 source data is identified as “all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.” This is the first recording of subject-related information. According to 21 CFR 312.62(b), and investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual. Source documents must be complete, accurate, and valid. The regulatory authorities consider source documents to be the basis for al trial data and the adjudication of the outcome of events. The purpose of source documents/patient record binder:

- To document the existence of the participant and substantiate integrity of trial data collected.
- To include original documents related to the trial, medical treatment, history of participant, and participant’s condition while on-study or in follow-up.
- To provide an auditable link in the chain from the study database back to the original source (visit worksheet).
- To collect data for transfer to CRFs and then to the study database.
- To instruct study coordinators and other site personnel on what data to collect and information necessary to answer data queries.

These can be electronic media, original documents or certified copies. The following Source Document Binder Table of Contents is adopted from Partners Healthcare.

Tab	Documents	Reference

Informed Consent	• Written informed consent form to document that consent is:
	  ◦ Obtained in accordance with regulations, GCP, and protocol
	  ◦ Dated prior to participation of each subject in trial
	• HIPAA form
	• Subject Bill of Rights
		OHRP Informed Consent Guidance Information; ICH GCP E6 Section, 4.8

Tab	Documents	Reference
Records	• Includes but not limited to hospital, clinic and office records, progress notes, medical history, subject diaries, subject questionnaires unless accessible via EMR	ICH GCP E6 Section 1.5.1, 1.5.2, 8.3.13
Inclusion/Exclusion Checklist	• Documentation of subject eligibility to be part of the study	
Correspondence	• Notes to file, memos, correspondence, documentation of phone or email contact (all subject-related)	
Outside reports	• Laboratory, X-ray, CT, ECG, etc.	
Con Meds, AEs, SAEs	• Forms used to collect and document adverse events, concomitant medications, serious adverse events, etc.	

Case Report Form (CRF) Binder/Electronic Case Report Form (eCRF)

According to ICH GCP EC 1.11, a case report form is a printed, optical, or electronic document designed to record all of the protocol required information to be reported on each trial subject. CRFs are designed by the sponsor or sponsor-investigator and maintained at the investigative site. Information documented on the CRF (or eCRF) must be supported by source documentation. At a minimum the CRF should record:

- Inclusion/exclusion criteria and assessment as to whether the subject met them
- Protocol-specific clinical laboratory testing (including EKGs, X-rays, eye exams, scans, etc.) documented by laboratory records
- All AEs, SAEs, concomitant therapies, and/or inter-current illnesses
- Assessment of severity of AEs, relationship to test article, and expectedness of the AE
- Report of all dropouts and the reasons

One of the most essential tasks performed by the Clinical Research Coordinator (CRC) is completing and/or ensuring the completion of the subject's CRF. Most sponsors will provide instructions or a guide for CRF completion. Handwriting must be legible and should be completed in black ink. All data points must be addressed and for fields that cannot be completed, "not available," "not done" or "unknown" should be marked in accordance with the sponsor's instructions. The CRC will ensure that all required data are collected and entered on the CRF as soon as possible after, if not during, the visit. All CRFs should be checked for completeness and legibility. The CRFs should be reviewed and signed by the investigator prior to submission. Only those physicians identified on the 1572 may sign CRFs. When making a correction on a CRF, a single line should be drawn through the incorrect entry and the correct data should be entered above or next to the incorrect entry. The correction should be dated and initialed. White-out or eraser should never be used to correct an error. Blanks identified prior to the investigator's review and sign-off on the CRF can simply be completed. Those identified after sign-off must be dated and initialed.

Study Financial Binder

An electronic copy of the financial documents is kept in the individual study network folder. Studies are organized by department then by Investigator. The Controller's office maintains electronic copies of all documents which include check copies, invoices, budget documents, etc. The documents in the network folder are kept separately from the negotiation items.

The following is an outline of the documents that should be kept in the financial binder:

Tab	Documents
Contract	• Billing grid and contract notes • Site agreement with sponsor, includes contract language and sponsor • LOI (if available) • Statement of Award Page • Lawson ID Request (hospital accounting)
Income	• Copies of all checks and ACHs that were applied to the account
Expense	• Copies of all monthly procedure reports (research services charges) • Any entries made to the account • Copies of participant travel/stipend forms
Other Miscellaneous Items	• Budget/fund establishment emails
Monthly Financial Statements	• These are located in a separate folder outside the study, organized by department or investigator

Tab	Documents
Patient Tracker	• Accounting of completed procedures/visits by each patient (Monthly Procedure Reports and activity logs) on the study and rolled-in summary of all patients on the study • Account of Receivables (money owed by a Sponsor based on the completed events)
Invoices	• Copies of invoices • Invoices generated in sponsor format based on the receivables
Budget	• Internal budget (IBBW or Budget Summary) which includes budget summary and budget detail

IND/IDE Binder (If Study Conducted Under IND or IDE)

Tab	Documents	Reference
FDA (if study conducted under and IND or IDE)	**Clinical Investigator (individual who conducts the study)** • FDA 1572 (drug) (The form FDA 1572/Investigator Agreement identifies the facilities where the research will take place, the reviewing/ approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation.) • Investigator Agreement (device) • Serious Adverse Event reports submitted to Sponsor **Sponsor-Investigator (individual who initiates and conducts the study)** • FDA 1572 (drug) (The form FDA 1572/Investigator Agreement identifies the facilities where the research will take place, the reviewing/ approving IRB and sub-investigators participating in the study. The 1572 should be updated if changes are made during the course of the investigation.) • Investigator Agreement (device) • Original application and all subsequent submissions to the FDA: ◦ IND Application (drug) ◦ IDE Application (device) ◦ Amendments to the Application ◦ Adverse Event Reports ◦ Annual Reports • Form 3674 (Certification of Registration to ClinicalTrials.gov) • Financial Disclosure forms	21 CRF 312 and 812; ICH GCP E6 Section 4.1

Prepare for Audits

An audit is a systematic and independent examination of trial-related activities and documents to evaluate whether the trial-related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, Sponsor's SOP, GCP and other applicable regulatory requirements. Auditors collect evidence and compare against standards, review documents, assess deviations and non-compliance and recommend actions.

FDA Inspections

The Bioresearch Monitoring Unit of the FDA may conduct inspections of medical research and testing facilities in order to ensure studies avoid bias and follow proper testing procedures.

The FDA inspector will review all case study data and may interview subjects and doctors. In all types of inspections, an FDA inspector checks the study for errors that affect the outcome.

Investigators may expect the following types of inspections:

- Routine Inspection may be conducted at random. It is sometimes triggered by abnormally high enrollment rate as well as large studies to promote a pivotal drug.
- For-Cause Inspections: FDA investigator has a reason to check out a research facility, i.e., subject complaint, a highly publicized drug, unqualified investigators, large AE clustering.

Once you receive notification of the FDA audit notify the appropriate research administration offices and IDS. Specific procedures to follow when preparing for an inspection and on the day of the inspection will be discussed with the research team prior to the inspection date and are outlined in the Standard Operating Procedures for Clinical Research, QA 601.

See details via the Clinical Trials Office (/cto).

Also, see FDA guidance (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-inspections-clinical-investigators) on FDA Inspection of Clinical Investigators for details.

Office of Research Quality Assurance (RQA)

Office of Research Quality Assurance (RQA) fulfills the auditor role for investigator-initiated studies. These audits are called Post Approval Reviews (PAR).

RQA conducts for-cause/directed reviews (requested by the IRB), random/routine reviews and self-evaluation assessments. The purpose of routine/random reviews is to assist investigators with achieving high quality of regulatory compliance. The reviews are meant to be more educational rather than punitive in nature.

RQA summarizes and reports the findings directly to the investigators. Investigators are required to submit all directed PAR reports to the IRB and significant findings in other PAR reports according to IRB Reportable New Information (RNI) reporting policy.

See RQA (https://research.med.psu.edu/rqa) details.

Audit Preparation and Assistance

If you have concerns about your preparedness for an audit, please contact the RQA office. RQA offers audit readiness assessment for both industry and investigator-initiated studies. This program helps ensure compliance with FDA, GCP, and IRB regulations, and institutional SOPs and policies and procedure as related to clinical research. The results of the pre-audit assessment will be provided for investigators and teams. For further information, contact RQA.

Billing and Invoicing

Verify Expenses and Income for Clinical Research Account

On a monthly basis the expense and income should be verified for the clinical research account. Reports are available via SIMBA, ran by the College of Medicine Research Accountant Supervisor. The COM Research Accountant, Department Financial Analyst and members of the study team should be certain that effort is being applied appropriately and that all income due is being tracked. The income and expenses in the accounting system should match the participant tracking document and any reports generated by hospital finance.

Maintain Log of Completed Study Procedures for Billing/Invoicing Reference

Within two business days, the study team is to enter participant visit information into STAR (https://research.med.psu.edu/research-support/star/). In the event a research visit will take multiple days to complete, the study team should create the visit in STAR and record the date of the activities as they occur. The study team should not mark the visit as “completed” until all applicable items/services have been done. Since Patient Financial Services (PFS) is primarily focused on completed visits, it is recommended that the study team send the following message to PFS through STAR (edit as needed):

For this study, the XXX visit(s) will take place over an extended period (possibly xx weeks). I will keep the visit(s) updated and open as a snapshot of what has been done and what hasn’t occurred yet. I will not finalize the visit until it has been completed. Please feel free to call if you have any questions.

The study team should be reviewing the contract notes and notifying the financial contact of any events that require an invoice or any other items of interest.

FOR LEGACY STUDIES (STUDIES NOT IN STAR)

On a weekly basis, the study team should enter the necessary visit information into the participant tracking Excel spreadsheet (on the shared network drive) and send to PFS and the central Financial Analyst (FA).

In the log, the first three columns should be filled out as listed. The rest of the columns, except for “Notes,” should be used to list the appropriate dates for that study. Any screening fails should be listed in notes and the appropriate subsequent dates grayed out. For questions filling out this Excel sheet, contact the Clinical Trials Office (https://research.med.psu.edu/research-support/clinical-trials-office/#topic-contacttheclinicaltrialsoffice). A central FA uses this information to convert completed visits into Receivables by using the contracted amounts per visit/procedure. All costs for rescheduled visits, delayed procedures, adverse events and any other “invoiceable” items are also captured at this time.

In the event a research visit will take multiple days to complete, the study team should send the above referenced message PFS by email to PFS_ClinicalResearch_Billing@pennstatehealth.psu.edu (mailto:PFS_ClinicalResearch_Billing@pennstatehealth.psu.edu), notifying them of the extended visit period.

Prepare Invoices for the Sponsor

The COM Research Accountant should invoice the sponsor on a monthly or quarterly basis dependent upon the contract terms. The study team should collaborate with the COM Research Accountant in order to make sure all appropriate items are being invoiced. Communicate with the COM Research Accountant for more details in regards to invoices.

Application of PI Salary Effort

PI effort will be reviewed at a minimum of quarterly and applied where appropriate, in a timely manner, in accordance with the internal budget and subject accrual or protocol activity.

The following is to be used to determine what document is be used as the internal budget:

(**Funding source:** Document)

Grant: Budget document submitted as part of the grant application
Industry contract: Budget Worksheet created by Clinical Trials Office
Departmental funds: Department-specified document

Effort will be charged based on prorated accrual, not based on income received. Adjustments of actual effort vs. budgeted effort may not be greater than a 25 percent change, unless there is a contractual amendment to the agreement. Salary Assignment Schedules will be reviewed at a minimum of quarterly and updated to reflect appropriate effort, where applicable.
For additional details, refer to the following policies:

- Policy: RAG64, Salary Caps (https://policy.psu.edu/policies/rag64)
- Policy: RA30, Facilities and Administrative (F&A) Costs (https://policy.psu.edu/policies/ra30)

Study Closure

SIMBA Account Closure

Account Closure or Extension Forms (ACE Forms) are sent to the COM Research Accountant when an account has an end date in the accounting system. The Controller's office receives a restricted fund report from Research Accounting at University Park with accounts that have end dates. The COM Research Accountant works with the investigator and study team to either extend the end date if the contract allows, request an amendment from the sponsor or close out the account in the accounting system. Communicate with the COM Research Accountant in order to obtain more details about the closure or extension of an account.

IRB Notified about Permanent Study Closure

To request study closure, click "Create Modification/CR" in the CATS IRB system, answer the questions on each screen, attach all requested supplements and submit it to the IRB Office. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Reference the Investigators Manual (HRP-103) in the CATS IRB Library for further information.

Investigational Drug Service (IDS) Pharmacy Notified about Study Closure

At the end of a trial, a close-out visit must be arranged by the study monitor. The monitor will perform the final drug reconciliation. The perpetual inventory will be "zeroed out" and the drug will be disposed of/mailed back per protocol. Copies of drug accountability records will be provided to the study monitor, which may be done by allowing the monitor access to Vestigo. Original records will not be released to the study monitor unless written permission from the study sponsor is obtained/provided by the study monitor. Once a study has been officially closed to accrual and all subjects at our institution have completed therapy with the supplied medication, the sponsor must perform final drug reconciliation within 30 days. After 30 days, any remaining drug will be destroyed per policy PAM 1406 (Investigational Drug Services: Destruction of Investigational Drugs.) Refer to the IDS section of this guidebook for additional information.

Office of Research Affairs (ORA) Notified

Once the project is terminated by the sponsor or the contract end date expires, the Controller's Office receives a monthly report from Research Accounting. The Controller's Office notifies the appropriate financial administrator for closeout or extension and provides an Account Closeout/Extension (ACE) form for completion. Once the financial administrator returns the ACE form to the Controller's Office, the Controller's Office notifies ORA of the expiration. ORA updates the SIMS database. Contracts must retain the agreement for the period of time designated in the agreement or if not so designated the period legally required The PI and department must retain the project records for the period of time designated in the agreement.

Documents Archived

For drugs, according to 21 CRF 312.62(c), an investigator shall retain records required to be maintained under the part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the applications is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

For devices, according to 21 CRF 812.140(d), an investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of two years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

Study Sponsors may have additional document retaining provisions stipulated in the Contract.

See details via the Clinical Trials Office (/cto).

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RESOURCES ABOUT COMPLYING WITH THE NIH PUBLIC ACCESS POLICY

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