GENERAL CLINICAL RESEARCH ORIENTATION AND RESOURCE MANUAL

VERSION MARCH 2024

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1 WELCOME AND INTRODUCTION

Welcome to the Center for Cancer Research (CCR)! Whether you are a federal employee or a contractor, we are excited to have you join our team. The orientation and educational needs of our clinical research staff can be complex due to the level of knowledge necessary to fulfill the various roles on our research teams. The main roles in the CCR are:

- Investigators including physicians and PhDs
- Physician Assistants
- Nurse Practitioners
- Clinical Research Coordinators – Nurses and non-nurses
- Data Managers
- Patient Care Coordinators
- Protocol Support Office Staff

This manual was developed as a central general orientation for our clinical research staff regardless of your role. Others who may benefit from this manual include Research Assistants, IRTAs and other clinical research team members not identified in the above list. It will help guide you through various orientation requirements and provide general clinical research information. Each section of the manual includes general content, additional resources, and recommended activities for new staff. In addition to this manual, there are role specific manuals for clinical research coordinators with manuals for patient care coordinators and advance practice providers under development. For the purposes of this manual, the terms "study team" and "research team" will be used interchangeably.

2 OVERVIEW OF THE NIH AND THE INTRAMURAL PROGRAM

The National Institutes of Health (NIH) is one of five health agencies of the Public Health Service (PHS), which, in turn, is part of the U.S. Department of Health and Human Services (DHHS). NIH is one of the largest research centers in the world and is the principal medical research arm of DHHS. NIH conducts basic, clinical, and applied research related to a broad spectrum of diseases and health problems. It represents the public's commitment to biomedical research and improving the health of its people.

The mission of the NIH is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability through basic and clinical research. The goals of the NIH are:

- to foster fundamental creative discoveries, innovative research strategies, and their applications as a basis for ultimately protecting and improving health;

- to develop, maintain, and renew scientific human and physical resources that will ensure the Nation's capability to prevent disease;
- to expand the knowledge base in medical and associated sciences in order to enhance the Nation's economic well-being and ensure a continued high return on the public investment in research; and,
- to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

NIH is made up of 27 Institutes and Centers (I/C). The Director of the NIH is a presidentially appointed position. The current Director is Dr. Monica M. Bertagnolli. The NIH invests about $41.7 billion annually in medical research for the American people. More than 80% of NIH's funding is awarded for extramural research (i.e., research conducted by scientist/investigators not employed by the NIH), largely through almost 50,000 competitive grants to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state. About 10% of the NIH's budget supports projects conducted by the scientist/investigators employed by the NIH (i.e., intramural research). There are nearly 6,000 scientists in the intramural research program. The main campus of NIH is in Bethesda, Maryland.

2.1 OFFICE OF INTRAMURAL RESEARCH

The Office of Intramural Research (OIR), housed within the NIH Office of the Director, is responsible for oversight and coordination of all intramural research, training, and technology transfer activities. The OIR also develops and implements NIH-wide projects, policies, standards, and review for intramural research, training, and technology transfer. Dr. Nina Schor, Deputy Director for Intramural Research, leads this office.

The Intramural Research Program (IRP) is conducted on several dedicated NIH campuses across the country. Although the IRP constitutes a small fraction of the total NIH budget, our facilities and funding structure provide us with a distinctive research environment. The IRP is able to leverage the extensive resources and expertise across the IRP to perform truly interdisciplinary research from the bench to the bedside. The IRP is also well-positioned to capitalize quickly on new scientific opportunities. Within the framework of the overall NIH mandate, the IRP mission is to:

- Conduct distinctive, laboratory, clinical, behavioral, translational and population-based research that breaks new ground and defines scientific excellence
- Facilitate new approaches to improve health through prevention, early detection, diagnosis, and treatment by developing and/or using innovative technologies, approaches or devices
- Respond rapidly to critical public health needs
- Train the next generation of biomedical and behavioral researchers
- Foster sharing of information and dissemination of the IRP's major discoveries to the public through partnerships with academic institutions and industry.

The IRP is the largest biomedical research institution in the world and includes the National Library of Medicine. There are approximately 1,200 Principal Investigators and more than 4,000 Postdoctoral Fellows conducting basic, translational, and clinical research. Its unique funding environment means the IRP can facilitate opportunities to conduct both long-term and high-impact science that would otherwise be difficult to undertake. More than 50 buildings on NIH campuses are devoted to the research enterprise, from state-of-the-art animal care facilities to homes for 7-Tesla MRIs and confocal microscopes, to a neurosciences cluster designed to foster collaborations across disciplines.

2.2 THE NIH CLINICAL CENTER (CC)

The Clinical Center (CC), opened in 1953, is the research hospital for the NIH and is the world's largest hospital devoted exclusively to clinical research. Its role is to support clinical research done by all the other NIH Institutes and Centers, as well as to conduct research done by its own staff. The Clinical Center is an accredited hospital with state-of-the-art facilities, excellent nursing and medical care. It also provides a unique array of patient services, such as the Children's Inn, Family Lodge and many more.

Currently, there are over 1,500 clinical research studies in progress at the NIH Clinical Center. About half are studies of the natural history of disease, especially rare diseases, which often are not studied anywhere else. What researchers learn by studying rare diseases often adds to the basic understanding of common diseases. Most other studies are clinical trials, which often are the first tests of new drugs and therapies in people. The clinical trials at the NIH Clinical Center are predominantly Phase I and Phase II, often first-in-human to test safety and efficacy.

The governance of the CC includes:

- Hospital Board: The hospital board is composed primarily of external advisors. The scope of the board is to advise the Clinical Center's performance, including management, finances and quality; requirements for hospital leadership and gaps in expertise; and policies and organizational approaches that promote quality and patient safety.
- Boards of Scientific Counselors: The purpose of this Board is to secure unbiased and objective evaluations of the intramural research programs and work of individual scientists. Expert scientists from outside NIH participate as members of this review group. The Board of Scientific Counselors of the Clinical Center was established in October 1990. The Board advises the NIH director, NIH deputy director for intramural research and the Clinical Center director regarding the organization's intramural clinical research programs though periodic visits to the laboratories to assess the research, progress, evaluation, productivity, and performance of staff scientists.

- Medical Executive Committee (MEC): The MEC advises the Clinical Center chief executive officer on the clinical aspects of operations and develops policies (i.e., Medical Administrative Series [MAS]) governing medical care standards in the Clinical Center. The committee is made up of clinical directors of the NIH intramural clinical research programs.
- Patient Advisory Group (PAG): A major source of patient feedback is the Patient Advisory Group, a forum established in 1998 and open to all patients and their families. The PAG meets semiannually, and as needed, with the chief executive officer of the Clinical Center and senior staff to discuss issues of concern and make recommendations to improve efforts for providing the highest quality research and patient care services.

Key CC leadership staff include:

- Chief Executive Officer: James K. Gilman, MD
- Chief Operating Officer: Pius A. Aiyelawo, FACHE
- Executive Officer: Ila Anita Flannigan, MHSA, FACHE (acting)
- Chief Medical Officer: Colleen Hadigan, MD, MPH
- Chief Financial Officer: Snul Vasudevan, ME, MS
- Chief Nurse Officer: Barbara Jordan, DNP, RN, NEA-BC
- Patient Representative: Antoinette (Toni) Jones, MSOD, RN
- Chief Scientific Officer: Leighton Chan, MD, MPH (acting)

To learn more about the CC visit: https://clinicalcenter.nih.gov/about1.html.

2.2.1 NURSING AND PROCEDURE UNITS

The nurses in the CC are referred to as Clinical Research Nurses (CRNs). They provide wide ranging support for intramural protocols through activities such as:

- Clinical care in support of patients participating in research
- Patient education about the research protocols
- Data collection, entry and analysis
- Investigational drug administration
- New idea generation and clinical study design
- Dissemination of research findings.

Below is a list of CC units and departments that mostly commonly serve patients in the CCR:

- Oncology Inpatient:
    - 1NW: Pediatrics
    - 3NE: Adult Hematology-Oncology & Blood and Marrow Transplant
    - 3NW: Adult Oncology
    - 3SEN: Medical Oncology/Hospice
- Oncology Ambulatory Care:

    - Pediatric Clinic (1H)
    - Radiation Oncology (B3)
    - Oncology (OP3)
    - Medical Oncology Service (OP12)
    - Developmental Therapeutics/Neuro-oncology (OP13)
- 3SES: Hematology-Oncology Day Hospital
- 3SWS: Intensive Care Unit (ICU)
- 3SWN: Procedure Unit

2.2.2 CLINICAL CENTER HEALTH INFORMATION MANAGEMENT DEPARTMENT (HIMD)

The Health Information Management Department provides medical record services to ensure medical records that are accurately documented in a timely manner, are readily accessible and permit prompt retrieval of data. Medical records are maintained for every inpatient and outpatient and must contain sufficient information to identify the patient, support diagnoses, justify treatment, and document results accurately. The Health Information Management Department also provides release of medical information services in accordance with the Privacy Act of 1974.

The Clinical Center's Health Information Management Department is comprised:

- Office of the Chief led by Tricia Coffey, MS, RHIA, CPHIMS, CPHI
- Medicolegal led by Amanda Grove, RHIA
- Record Processing led by Linda D. Williams, MHA, RHIA
- Documentation Analysis led by Samuel H. Nieves-Betancourt MD, CPC, CPMA
- Coding and Abstracting led by David Rice, RHIA, CCS

The HIMD handbook summarizes policies and procedures pertaining to medical records, including minimum documentation requirements for inpatients and outpatients. In addition, the handbook identifies the rules governing access to medical records and medical information at the NIH Clinical Center. The handbook is designed as a reference guide for health care professionals who participate in patient care and who are expected to abide by the regulations contained therein. The rules and regulations in this handbook are drawn in compliance with the policies of the Medical Executive Committee, Federal regulations including the Privacy Act of 1974, and Joint Commission standards. Suggestions for changes in the rules and regulations summarized in this handbook are welcomed and encouraged and should be submitted in writing to the Chief of the Health Information Management Department.

2.3 OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS (OHSRP)

Under the direction of Dr. Jonathan Green, the Office of Human Subjects Research Protections (OHSRP) carries out the day-to-day operations and regulatory oversight of human research activities within the Human Research Protections Program (HRPP) at the NIH IRP. The OHSRP promotes the protection of rights, safety and welfare of human subjects. It also promotes the NIH's research mandate by:

- Supporting the Intramural Research Program (IRP) in reviewing, administering and managing human subjects research activities
- Developing NIH policies and procedures consistent with federal regulations and policy
- Organizing and conducting educational activities for NIH HRPP investigators, research staff and the NIH IRB; and
- Overseeing quality assurance and quality improvement activities to ensure NIH Institutional Review Board (IRB) compliance with federal regulations and policies.

There are 3 key offices in OHSRP:

- The Office of IRB Operations (IRBO) oversees the day-to-day operations of the National Institutes of Health (NIH) Institutional Review Board (IRB). The NIH IRB meets 4-6 times per week and is comprised of at least five members of varying backgrounds in order to provide complete and adequate review of human research and its institutional, legal, scientific, and social implications. The Board also includes at least one member who is not affiliated with the NIH and one member who is not a scientist. The NIH IRB has several consultants who advise the Board and are periodically involved in protocol review.
- The Office of Compliance and Training is responsible for coordinating review and management of Reportable Events that occur during the conduct of Intramural Research Program (IRP) human subjects research (HSR) activities. Other responsibilities of the Office of Compliance and Training include:
    - Addressing administrative aspects of monthly meetings of the Research Compliance Review Committee (RCRC), which is a duly convened NIH IRB with nine specific members that reviews research related events that rise to the level of possible serious and/or continuing noncompliance
    - Reporting the following IRB determinations to the HHS Office of Human Research Protections (OHRP) and the FDA: unanticipated problems, serious and/or continuing noncompliance, and suspension or termination of research by the NIH Institutional Review Board (IRB)
    - Conducting noncompliance investigations, as needed
    - Quality Assurance (QA)/Quality Improvement (QI) reviews of NIH IRB activities
    - Responding to questions related to the training required for investigators who conduct human subjects research overseen by the NIH IRB

    - Creating HSR related educational materials for NIH investigators and staff and coordinating monthly OHSRP Education Series sessions.
- The Office of Policy and Accreditation is responsible for:
    - Establishing Human Research Protection Program (HRPP) policy for the Intramural Research Program (IRP), maintaining the HRPP Policy Glossary and developing educational materials about the policies. The HRPP policies are part of the OMA policy System (Manual Chapter 3014 - NIH Intramural Human Research Protection Program) and can be found on the OHSRP policy webpage along with the educational materials about the policy series.
    - Maintaining accreditation of the NIH IRP HRPP. NIH is accredited by the Association for Accreditation of Human Research Protection Programs (AAHRPP). This accreditation is an indication that the NIH prioritizes human subjects research that protects the rights, safety and welfare of its research participants. Accreditation is a commonly accepted indicator of quality and excellence, important both to potential research participants and to our scientific collaborators.

2.4 ADDITIONAL RESOURCES

- NIH video about the past, present and future (5 minutes)

3 OVERVIEW OF THE NATIONAL CANCER INSTITUTE (NCI)

The National Cancer Institute (NCI) is the federal government's principal agency for cancer research and training. The mission of the NCI is to lead, conduct, and support cancer research across the nation to advance scientific knowledge and help all people live longer, healthier lives. The NCI leads the nation's research efforts to improve cancer prevention, detection, diagnosis, and survivorship. The NCI:

- Supports NCI-Designated Cancer Centers and more than 5,000 grantees
- Coordinates and supports all phases of clinical trials across 2,500 clinical trial sites nationwide, seeking the development of new and improved cancer treatments
- Partners with industry, private philanthropic organizations, other federal agencies, and other national and foreign institutions to engage in cancer research and training opportunities that otherwise might not be possible because of their complexity and cost.
- Collaborates with private-sector life sciences companies to advance promising innovative technologies that fuel improvements in detection, diagnosis, and treatment of cancer
- Provide training and support for cancer researchers through funding, training, and career development opportunities.

The Director of the NCI is a presidentially appointed position. Our current is Dr. Kimryn Rathmell. The NCI has both intramural and extramural divisions/centers. NCI Intramural consists of the:

- Center for Cancer Research (CCR)
- Division of Cancer Epidemiology and Genetics (DCEG)

The 5 extramural divisions include:

- Division of Cancer Biology (DCB)
- Division of Cancer Control and Population Science (DCCPS)
- Division of Cancer Prevention (DCP)
- Division of Cancer Treatment and Diagnosis (DCTD)
- Division of Extramural Activities (DEA)

Visit each of the websites above to learn more about the divisions and centers that make up the NCI. To learn more about history of the NCI visit https://www.cancer.gov/about-nci/overview/history. NCI's main website is https://www.cancer.gov/.

4 OVERVIEW OF THE CENTER FOR CANCER RESEARCH (CCR)

The Center for Cancer Research (CCR) is the basic and clinical intramural research program (IRP) of the National Cancer Institute (NCI) at the National Institutes of Health (NIH). The CCR is the largest division of the NCI's intramural research program with nearly 250 basic and clinical research groups located on two campuses – Bethesda, MD and Frederick, MD. Our scientists work on a wide spectrum of biological and biomedical problems ranging from visualizing and understanding the structure of individual genes and proteins, developing novel methods for drug discovery, to inventing biomedical devices and technology and creating innovative ways to treat patients in the NIH Clinical Center.

The mission of the CCR is to improve the lives of all cancer patients by solving important, challenging, and neglected problems in cancer research and patient care through:

- A world-leading basic, translational, and clinical research and patient care program
- An institutional focus on high-risk and long-term projects, unmet needs, and pursuit of unexplored ideas
- Research to eliminate cancer health disparities
- Leadership and coordination of national disease networks and development of technology resources for the cancer community
- Partnerships with academic institutions, commercial entities, and patient advocacy groups
- Training of the next generation of a diverse and inclusive biomedical workforce.

The Acting Co-Directors of the CCR are Dr James Gulley and Dr. Glenn Merlino. CCR has over 50 branches/labs/programs that accomplish the mission of the CCR. To learn more about the various branches/labs/programs in the CCR, please visit: https://ccr.cancer.gov/clinical-trials/lab-branch-program-directory; select your branch, lab or program to learn more. The CCR's current clinical portfolio consists of over 400 clinical protocols of which 70% are clinical trials with the remaining protocols being observational studies.

4.1 OFFICE OF THE CLINICAL DIRECTOR (OCD)

Each I/C in the NIH IRP that has a clinical program is required to have a Clinical Director (CD) and an Office of the Clinical Director (OCD). The Office of the Clinical Director serves as the interface between CCR clinical investigators and the NIH Clinical Center where CCR clinical trials take place. The Clinical Director for CCR, Dr. James Gulley, oversees and assures the quality of medical care delivered to patients treated on CCR clinical trials. The OCD supports CCR's clinical research program by providing:

- Biostatistical expertise for clinical trial design and analysis
- Administrative support for the protocol review and monitoring process
- Training and continuing education for clinical research staff
- Data management, auditing and monitoring of NCI intramural and multi-institutional trials
- Informatics for data collection and storage.

To learn more about the CCR, visit https://ccr.cancer.gov/, specifically the Clinical Research Operations site.

4.1.1 OFFICE OF RESEARCH NURSING (ORN)

The Office of Research Nursing (ORN) is under the direction of Corrine Keen and supported by seven supervisory research nurse specialists (Team Leads). The ORN is responsible for providing a unique, cohesive team of superior research nurse specialists, non-licensed clinical research coordinators and patient care coordinators to carry out the mission of the CCR through a culture that supports continuing education, mentorship, professional development, and collaboration while balancing comprehensive patient coordination and quality clinical and translational research.

Main responsibilities of the ORN:

- Recruitment of research nurse specialists, non-licensed clinical research coordinators and patient care coordinators.

- Ensuring quality orientation and mentorship to new employees in collaboration with the CCR Office of Education and Compliance.
- Collaborating with research teams to assess workload and propose staffing plans to meet team's needs.
- Providing leadership and support to staff on a day-to-day basis in the performance of their duties.

4.1.2 OFFICE OF EDUCATION AND COMPLIANCE (OEC)

The Office of Education and Compliance (OEC), under the direction of Elizabeth (Liz) Ness provides clinical research training and the compliance activities for the CCR's clinical research staff (e.g., clinical investigators, study coordinators, data managers, patient care coordinators, administrators, and support staff). The main responsibilities of OEC are to:

- Coordinate, develop and evaluate orientation programs for clinical research staff
- Coordinate, develop, and evaluate on-going educational programs. The programs relate to clinical research and clinical trials including regulatory components, data management and the roles and expectations of the research team
- Coordinate, develop, and evaluate the CCR's comprehensive clinical research quality management program in accordance with the requirements of regulatory and accrediting organizations (e.g., FDA, OHRP, Association for the Accreditation of Human Research Protection Program); DHHS and NIH policies, practices, and procedures, and state of the art practices for quality assurance and clinical research. This includes:
  - Developing and maintaining CCR clinical research SOPs
  - Auditing of non-IND treatment trials and observational trials
  - Assisting in the development of Corrective and Preventive Action (CAPA) plan
  - Assisting with site visits and FDA inspections
  - Providing consultative services related to clinical research

4.1.3 PROTOCOL SUPPORT OFFICE (PSO)

The goal of the Protocol Support Office (PSO), under the direction of Stacie Jeter, is to standardize and streamline regulatory operations for CCR's clinical research protocols. The PSO provides the following support services for CCR Investigators:

- Protocol navigation through various reviews and approvals from scientific review through IRB closure
- Regulatory coordination through the lifecycle of the protocol, including:
  - Protocol writing
  - Consent writing
  - Genomic data sharing determinations
  - Regulatory coordination for multi-center studies
  - Interface with pharmaceutical collaborators

    - Maintenance of the investigator regulatory files
- Collaborative coordination with:
    - Pharmaceutical companies
        - Facilitate protocol/amendment review
        - Provide IRB approvals/documentation
    - Cancer Therapy and Evaluation Program (CTEP)
        - RCR (Registration and Credential Repository) coordination
        - IAM (Identity and Access Management) account management
    - NCI Technology Transfer Center
        - Provide cursory review of Tech Transfer agreements (e.g., CTAs, CRADAs)
- Communication with Office of Sponsor and Regulatory Oversight (OSRO) on IND/IDE studies:
    - Facilitate OSRO determination/input on all initial protocols and amendments
    - Format and prepare all initial protocols and amendments for FDA submission by OSRO
- Management of key CCR ancillary review committees:
    - Scientific Review Committee (SRC)
    - Safety Monitoring Committee (SMC)

4.1.4 OFFICE OF CLINICAL RESEARCH SUPPORT SERVICES

The Office of Clinical Research Services, under the direction of Allison Wise, provides support services data management, monitoring/auditing, information technology (IT) support, and QA. These services are provided by staff hired through a single contract dedicated to ensuring CCR clinical research staff have the resources and support to carry out their clinical trials. In addition, this office provides:

- A dedicated Contracting Officer Representative (COR) who provides contract management for OCD/CCR contracts
- Dedicated staff to represent OCD in space and construction projects
- Dedicated staff who provides coordination of CCR IT projects through the Change Configuration Management Group (CCMG)

The Office of Clinical Research Support Services provides the following support services for CCR Investigators:

- **Data Management**: Each team is provided data managers who are assigned protocols to conduct the following tasks:
    - Abstract, enter, and quality check data in the CCR and outside sponsor databases
    - Run reports from the databases
    - Assist preparation for monitoring and audit visits
    - Provide data management support for the CIBMTR

- **Monitoring/Auditing**
  - Eligibility and consent monitoring
  - Non-IND/IDE protocol monitoring and auditing
  - Other audits as requested by OCD

- **Clinical Database IT support**
  - Implementation, updating and maintenance of CCR database systems C3D, RAVE, reporting tools (Jreview), and users' manuals
  - Data transfers to outside sponsors and manufacturers
  - Collaborates with Office if Information Technology (OIT) coordinating OCD and OIT system interactions

- **Quality Assurance/Quality Check support**
  - Direct QC of Data and Clinical trials conduct by independent data review by QC specialists
  - QA/QC of functional contract areas: IT, data review, clinical monitoring/audit
  - Quality Improvement: Systemic collection and analysis of QC outcomes and development action plans for continuous improvement.

4.1.5 OFFICE OF SPONSOR AND REGULATORY OVERSIGHT (OSRO)

The Office of Sponsor and Regulatory Oversight (OSRO), under the direction of Dr. Shy Shorer, ensures CCRs regulatory compliance with sponsor obligations for Investigational New Drugs (IND) and Investigational Device Exemptions (IDE), a critically important role for the CCR clinical research program and its investigators. In addition, this office provides analytic support, leads the pharmacovigilance program, monitors clinical trials, and serves as the subject matter experts regarding FDA regulations.

4.1.6 OFFICE OF PATIENT-CENTERED OUTCOMES RESEARCH (OPCORE)

The goal of the Office of Patient-Centered Outcomes Research (OPCORe) is to integrate the voice of the patient, and in particular, the use of patient-centered outcomes into early-phase clinical trials. Both the National Cancer Institute and the Food and Drug Administration have noted the need for more systematic ways of gathering patients' perspectives on their condition and the impact of novel therapies on how they feel and function.

4.1.7 CLINICAL PHARMACOLOGY PROGRAM (CPP)

The mission of the Clinical Pharmacology Program (CPP) is to fully characterize the clinical pharmacology of new anticancer agents entering CCR clinics. Based within the Office of the Clinical Director, the CPP provides services and expertise to all CCR investigators and is the only

group available to CCR investigators for clinical pharmacology collaboration. Dr. William Figg has headed the CPP since its inception in 1992.

The CPP provides a range of services to support the conduct of clinical trials and serves as a resource for clinicians seeking advice on study design. To learn more, visit each of our four sections, below, to view and access available services.

- Biospecimen Processing Core (BPC)
- Pharmacokinetic and Pharmacometrics Section (PPS)
- Pharmacogenetics Section (PG)
- Clinical Section (CS)

4.2 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Bookmark the websites found here
2. View *Welcome to ROB: An Introduction to Radiation Oncology*, an Oncology Lunch & Learn from February 2024 for an overview of radiation oncology and the Radiation Oncology Branch (60 minutes)

4.3 ADDITIONAL RESOURCES

- CCR website: https://ccr.cancer.gov/
- List of NIH and research acronyms
- OHSRP website: https://irbo.nih.gov/confluence/display/ohsrp/

5 OVERVIEW OF ROLES & RESPONSIBILITIES

This section outlines the roles and responsibilities of various members of the research team.

5.1 INVESTIGATOR

An Investigator is an individual (i.e., physicians, PhDs, physician assistants, nurse practitioners and clinical research coordinators) who is involved in the conduct of human subjects research. Their involvement as defined in the regulations (i.e., 46 CFR Part 46, 21 CRF Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312, 21 CFR 812 Subpart E) would include:

- Obtaining information about living individuals by intervening or interacting with them for research purposes
- Obtaining identifiable private information or identifiable biospecimens about living individuals for research purposes
- Obtaining the voluntary informed consent of individuals to be subjects in research

- Studying, interpreting, or analyzing identifiable private information, biospecimens, or data for research purposes

Some research studies are conducted by more than one investigator, and one investigator is designated the Principal Investigator (PI). The Principal Investigator is the investigator with the overall responsibility for the design, conduct, and reporting of the research, and must assure both the protocol and the research team's actions are compliant with law, regulations, and NIH policy, even when certain aspects of the research are delegated to other investigators.

See HRPP Policy 300 *Investigators Responsibility* for the types of investigators at the NIH IRP and corresponding responsibilities.

To learn more about Investigators Responsibilities in the NIH IRP, read the *NIH Investigator Manual for Human Subjects Research* and view:

- *Responsibilities of the Principal Investigator Part 1: What You Need to Know & Do Before Your Protocol Starts*
- *Responsibilities of the Principal Investigator Part 2: Implementation of a Clinical Research Protocol*
- *NIH Investigator Seminar Series*

5.1.1 PI DELEGATION OF RESEARCH TASKS/ACTIVITIES

It is common for the PI to delegate certain study-related tasks or activities to employees, colleagues, or others. When tasks are delegated, the PI is responsible for providing adequate training and supervision of those to whom tasks are delegated. The PI is accountable for regulatory non-compliance resulting from failure to adequately train staff and/or supervise the conduct of the clinical study. Typically, the CRC will start and help maintain the Delegation of Activities (DOA) (previously referred to as the Delegation of Tasks (DOT) log for the PI and the monitor will review the log at each monitoring visit.

5.1.2 DELEGATION LOG

In the CCR, all research studies (interventional and observational) are required to have a DOA Log. The PI is responsible for ensuring the person to whom the task has been delegated has appropriate training, licensure and Clinical Center credentialing if appropriate to perform the task. Tasks delegated by the PI must be consistent with roles assigned in PROTECT and on the FDA Form 1572 if applicable.

In July 2023, the CCR updated the DOA log so that all signatures are digital. In addition, the CCR signature sheet was created to document a staff member's handwritten ("wet") signature and initials to allow comparison on research documents that require a

handwritten signature and/or initials. The signature sheet is not protocol specific so only one is required per staff member and they are valid for 5 years.

All CCR studies that do not have a sponsor must convert to this version of the log by June 1, 2025. To clarify moving from the old CCR DOT log to the new DOA log, teams should submit a note to file signed by the PI for the regulatory binder. PSO managers can provide a template.

To learn more about PI delegation and how to complete the CCR log and signature sheet, review:

- CCR SOP PM-1 *Delegation of Tasks for Research*
- Guidelines for Completing the Delegation of Activities Log
- CCR Delegation of Activities Log
- Guidelines for Completion of the CCR Signature Sheet
- CCR Signature Sheet

Please note that when working with an IND/IDE sponsor, the sponsor typically has their own log they want completed. This may be a paper or electronic log.

When CCR is the sponsor, use the OSRO *Clinical Site Delegation of Authority and Staff Signature Log*. There are instructions on how to complete the log on the first page of the document and a separate FAQ sheet. This log was updated in July 2023 so that all signatures are digital. OSRO is also using the CCR signature sheet to capture any required staff member "wet" signatures.

All OSRO studies that will still be open (active) on or after June 1, 2025 must convert to this version of the log by then. To clarify how to manage moving from the old ORSO DOA log to the new one, OSRO would like research teams to either enter end dates with PI initials/signature or submit a note to file signed by the PI.

5.2 REQUIRED TRAINING FOR ALL INVESTIGATORS

All members of the Research Team who are delegated research tasks by the PI will be required to complete the following Collaborative Institutional Training Initiative (CITI) training:

- Mandatory CITI Training (to be renewed every 3 years):
    - Click here to start navigating to the NIH CITI portal Log into your CITI account via the NIH portal. Then click on the CITI training tab to start. Please read the directions in the gray box on this website first.
    - Once you are logged in to the NIH CITI portal using your NIH log in, select *NIH View Courses*
    - Scroll down to *Add a Course*
    - Select *Biomedical 101* (this is human subject protection training) **and** *Good Clinical Practice US FDA Focus*

    - If you are involved with Social and Behavioral research, please complete the course *Social & Behavioral Research.*
        - Note, for staff conducting both biomedical and social/behavioral research, both courses are required.
    - Launch the required courses and complete
    - You will receive an email for each course completion with a link to the completion report and certificate, please forward to CCR OEC (NCICCROEC@mail.nih.gov). This will ensure that your certificates are also available for monitors.
    - Save a copy of your record and certificate for your files.
- Optional CITI Training (one time only):
    - If you will be working with children, please complete the course *Vulnerable Populations – Research Involving Children*.
    - If you will be working on studies that have a genetic or genomic component, please complete the course *Genetic Research in Human Populations*.

Additional training is required by the NIH IRP for all investigators:

- NIH Research Ethics: Complete the *Introduction to the Responsible Conduct of Research* course at https://researchethics.od.nih.gov/. Please keep the certificate for your records and send a pdf version to CCR OEC (NCICCROEC@mail.nih.gov).
- NIH Technology Training: See the *NIH Technology Transfer Training Guidance* for accessing the course.

5.3 NURSE PRACTITIONER/PHYSICIAN ASSISTANT

Nurse Practitioners (NPs) and Physician Assistants (PAs) serve a variety of roles on research teams. Their main responsibility is managing clinical care of research participants. As investigators on studies, they are also required to follow NIH policies and regulations regarding the conduct of clinical trials. The following is a brief overview of typical NP/PA job duties and responsibilities:

- Manages clinical care (i.e., clinic visits, day hospital visits, inpatient admissions)
- Assists with patient triage
- New referral intake
- Obtains informed consent, if delegated
- Places clinical care CRIS orders including consults
- Coordinates tests, procedures, consults, etc. with the appropriate department(s) as well as CRC and PCC
- Documents in CRIS
- Coordinates with outside providers as needed to ensure patient safety and continuity of care

5.4 CLINICAL RESEARCH COORDINATOR

CRCs have many roles on a research team, as well as many names (e.g., Clinical Research Nurse, Research Nurse Specialist, Clinical Trial Nurse, Research Nurse Coordinator, Study Coordinator to name a few). The CRC spends most of their time managing the study by coordinating within the multidisciplinary team, communicating with referring physicians and providing for protection of human subjects. The CRC is accountable for both the research participant and the protocol. If the CRC is also a registered nurse, all general nursing responsibilities apply (e.g., documentation, drug administration, participant triage).

Below is a list of typical CRC job duties and responsibilities focused on management of clinical research participants and protocol compliance:

- Coordinates study in regards to:
    - Recruitment
    - Screening and ensuring participants have met eligibility criteria prior to enrollment
    - Securing informed consent
    - Scheduling participants for protocol-required visits, tests and procedures
    - Preparation for and facilitates initiation, monitoring and close-out visits
    - Coordination of lab pick-ups, supplies
- Maintains integrity of protocol
- Identifies facilitators and barriers to protocol compliance and seeks solutions in collaboration with the PI and rest of the research team
- Maintains essential documents and regulatory files
- Assists PI in preparing protocols and consents for initial review, modifications, and continuing review
- Identifies events that required expedited reporting to the IRB and/or Sponsor (e.g., serious adverse events, adverse events of special interest, major deviations, unanticipated problems, noncompliance, etc.) and ensures they are reported on time with appropriate corrective and preventative actions
- Maintains participant records & thorough documentation to support protocol requirements
- Educates other research team members and clinical staff regarding appropriate and accurate documentation
- Ensures that relevant data from source documents are abstracted and recorded in the clinical research study database and that every data point can be verified within the source document
- Collaborates with PI, pharmacy and others to ensure proper use of an accountability for study agents
- Provides and documents patient education
- Assesses the need for, helps develop and implements staff education

- Abstracts, analyzes & publishes findings with PI
- Stays informed (with PI) of new information regarding investigational agent
    - Investigators Brochure, Articles, IND Safety Reports, Memos
- Collaborates with team to resolve source documentation and data discrepancies
- Anticipates the deadlines and data needed for
    - IRB
    - Sponsor
    - FDA
    - Professional meeting abstracts
    - Audit/monitoring visits
- Mentors other CRCs

5.5 DATA MANAGER

See Section 4.1.4.

5.6 PATIENT CARE COORDINATOR

The role of the PCC varies depending on the needs of the individual research team. However, the following is a brief overview of typical PCC job duties and responsibilities:

- Communicates with new patients and their referring physicians to provide screening and ongoing trial related patient information
- Schedules and communicates with patients and research team for tests and appointments needed to meet protocol requirements
- Prepares travel, lodging, and admissions documents for patients
- Requests films and pathology samples
- Delivers outside films to Film Library
- Enters patient data into relevant Clinical Center systems
- Prepares, distributes, and files relevant documentation to research team and in research records and regulatory binders
- Provides overall tracking and coordination of study calendar/study status information for all patients on-study for the research team

5.7 PROTOCOL SUPPORT OFFICE STAFF

Refer to Section 4.1.3

5.8 RESEARCH PARTICIPANT

A research participant is referred to in the regulations as a human subject and this person voluntarily participates in clinical research after giving informed consent to be the subject of the research. Research participants (e.g., cancer patients, healthy volunteers) are a diverse

group of individuals who enter the research setting for a variety of reasons and who play important roles in the research process. For patients with cancer, participating in clinical trials provides access to research with the hope of extending survival time, greater access to healthcare professionals, and altruistic satisfaction. Effective communication of information is an essential prerequisite for enabling patients to make informed decisions about their care.

Individuals should understand their potential role as a research participant before agreeing to participate in a clinical research study (i.e., signing the informed consent document). Individuals should be encouraged to read the consent form thoroughly and write down questions for the investigator. They should be provided the time to take the document home and discuss the study with family, friends, or their personal physicians. If they do not understand any portion of the consent, they should be provided the opportunity to ask the investigator to further clarify the information. Individuals should never sign the consent document unless they believe that they understand its content and feel comfortable with their decision. The informed consent process may require multiple discussions between the individual and the investigator.

Other participant activities include:

- Respecting the research team and other participants
- Following directions for all protocol related procedures including those associated with self-administered study medications
- Knowing when the study begins and ends. This is particularly important for an intervention trial that has a follow-up period after the intervention is completed
- Arriving to scheduled appointments on time, or informing the staff within a reasonable time if they need to reschedule
- Providing truthful answers to questions asked throughout the study
- Informing the research team if other medical care is needed while on the study
- Informing the research team if there are questions that they would prefer not to answer
- Reporting pain, discomfort, nausea, dizziness and other problems and symptoms they experience during the study
- Keeping information about the study confidential, if asked to do so
- Keeping the research team informed when contact information changes
- Informing the research team if they decide to withdraw from the study and follow the appropriate procedures for withdrawal

Individuals who enroll in a research study should fully intend to comply with its requirements as explained to them during the initial informed consent process. The decision to enroll in research is a serious commitment and individuals who enter a study with the intent to change treatments if they do not like their treatment assignment, or those who know they are not likely to complete the study should not enroll. Failing to adhere to a study may expose the participant to unanticipated harm, invalidate the study, and expose other research participants to unnecessary risks, all of which can undermine a study's future benefits to others. It is the

responsibility of the PI and the research team to inform and reinforce to the participant their responsibilities. Also remember to document in CRIS these types of conversations.

5.9 PHARMACY

While the PI is ultimately accountable for drug accountability, this is often delegated to a pharmacist. Activities include:

- Preparing drugs as per protocol
- Storing investigational products as per protocol
- Providing separate/distinct storage in pharmacy for multiple studies using same IND
- Maintaining accurate drug accountability records
- Tracking and storing receipts of drug shipment/invoices
- Maintaining drug accountability record forms/database
- Designing, maintaining and updating drug order sets for protocols in CRIS

The CC pharmacy intranet site provides the following information:

- Formulary and drug information
- Pharmacy and Therapeutics (P & T) approved guidelines, lists and policies
- Hazardous drug resources
- Pharmacy newsletters
- Infusion pump information
- P & T committee
- Patient education
- Pharmacy services
- Departmental policies
- Protocol information
- Drug fact sheets

5.10 SPONSOR

According to Title 21 of the Code of Federal Regulations, a Sponsor is defined as "a person who takes responsibility for and initiates a clinical investigation. 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. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators."

Not all protocols in the CCR will have a sponsor (e.g., non-IND/IDE intervention protocol, tissue procurement, natural history, and other observational studies).

CCR serves as a sponsor. All sponsor related activities are overseen by the Office of Sponsor and Regulatory Oversight OSRO. Other sponsors that CCR may work with include NCI's Cancer Therapy Evaluation Program (CTEP), industry and the Clinical Center.

CCR staff must learn their sponsor's processes, including case report form (CRF) completion and answering queries, serious adverse event (SAE) and other reporting requirements, and monitoring visits. These topics are covered in other sections of this manual.

For more information, refer to the *Drug Development: Role of the FDA and Sponsor* online learning module.

5.11 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete the *Responsibilities of the Research Team* online learning module
2. View *Responsibilities of the Principal Investigator Part 1: What You Need to Know & Do Before Your Protocol Starts.*
3. View *Responsibilities of the Principal Investigator Part 2: Implementation of a Clinical Research Protocol*
4. Read CCR SOP PM-1 *PI Delegation of Tasks for Research*
5. Complete Signature Sheet, if needed, and submit to your PSO manager per the guidelines under CCR SOP PM-1
6. Identify the Sponsor for your protocol(s) (OSRO, CTEP, Industry, No Sponsor)
7. Complete the *Drug Development: Role of the FDA and Sponsor* online learning module
8. Learn team process for scheduling with OR, IR and 3SW-N Procedure Unit, if applicable
9. Review CC MAS Policy M95-9 Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center
10. Learn team process for scheduling phlebotomy, outpatient clinic and day hospital appointments

5.12 ADDITIONAL RESOURCES

- Resnik, D.B. & Ness, E. (2012). Participants' responsibilities in clinical research. *Journal of Medical Ethics 38*(12), 746-750.

6 ADMINISTRATIVE – CLINICAL RESEARCH

In addition to the Clinical Center's Medical Administrative Series (MAS) policies, there are two sets of policies and standard operation procedures (SOP) specific for clinical research:

1. NIH IRP Policies for human subjects protection
2. CCR Policies and SOPs

All research staff should bookmark both websites and familiarize themselves with those policies and procedures that affect their work.

6.1 ADMISSIONS, VOUCHER AND TRAVEL (ATV) SYSTEM

The NIH Clinical Center Admissions, Voucher and Travel (ATV) system is an electronic system used to request:

- Admission to the NIH Clinical Center (inpatient, outpatient and External Location)
- Government-arranged patient air/train travel
- Vouchers for patients –transportation, lodging and meals
- Patient demographic changes
- Reactivation of an old Medical Record Number (MRN)
- Financial assessments

For ATV training and account access see activity number 13 under CCR Orientation Activities.

The first time a patient comes to the Clinical Center they will need to first stop at the Admissions Office (located on the 1st floor) to finalize admissions paperwork. This includes a patient update form to update any demographics that may have already been submitted if they first went through the External Location process (see section 4.2). The patient update form should also be presented to them periodically at outpatient visits for any demographic changes. It is important to make sure that patients keep all demographics up to date as ATV/CRIS, the Patient Registration and Enrollment System (PRES), and the clinical database (i.e: Rave) all need to match. Patients should also be encouraged to provide timely updates related to contact information for themselves, and any outside physicians to maintain continuity of care and facilitate any protocol required follow up.

For more information, see CCR SOP ADCR-4 *Admission, Travel, and Voucher (ATV) Process*.

6.1.1 REIMBURSEMENT

During protocol development, the PI completes the Designation of Reimbursement of Travel and Subsistence (DRTS) form. This is based on the following:

- MAS policy M08-1 Reimbursement of Travel and Subsistence Expenses for NIH Clinical Research Protocol Participants

- CCR SOP ADCR-5 *Travel and Lodging Reimbursement for CCR Clinical Research Participants, Pediatric Guardians, and Authorized Attendants*
- Protocol and/or participant specific considerations

Approved reimbursement (as known as the most recent patient travel form) is listed under each protocol in the PROTRAK Query System (PQS). The research team should provide potential research participants information regarding travel and reimbursement during the referral process and throughout their research participation as a part of ongoing informed consent. For more information about PQS, see section 6.5.

If the research team would like to request an exception to the travel policy, they must complete the CCR Travel Policy Exception Request form and submit per CCR SOP ADCR-5.

6.1.2 COMPENSATION

Some studies offer compensation for research participation. The amount of compensation is guided by HRPP Policy 302 – Recruitment and Compensation. Informed consent documents must contain details regarding payment including type, amount and timing. If payment could equal or exceed $600 in a calendar year the IC document also needs to include the following language "With few exceptions, study compensation is considered taxable income that is reportable to the Internal Revenue Service (IRS). A "Form 1099-Other Income" will be sent to you if your total payments for research participation are $600 or more in a calendar year."

Research team members may enter compensation per protocol via the Research Volunteer System, which is maintained by the Office of Patient Recruitment (OPR). Team members will need to enter a CAN number for payment for each protocol, which can be obtained from the PI/branch. For more information about payment to research volunteers at the CC, please see OPR's Payment to Research Volunteers.

6.2 EXTERNAL LOCATION (EXT LOC) REQUIREMENTS

The Clinical Center has created a process for registering patients who are participating in intramural research studies, but may not be physically coming, at least initially, to the Clinical Center. These patients may be having radiology images read, outside records sent for consultation, specimens sent to Anatomic Pathology confirmation, or be a field cohort.

The process includes hospital consent forms with language appropriate to this type of patient 'visit'; streamlining the process for consenting, registering, and tracking patients at external locations; and developing a mechanism to ensure that any of these patients who may become on-site CC patients in the future are flagged and registered/consented accordingly.

Forms and instructions for submitting the EXT LOC ATV request can be found on the HIMD website. Spanish versions are also available.

When a patient is registered as an External Location patient to strictly have specimens analyzed or films read, the External Location Registration Note is required to be entered in CRIS. The note can be documented by any nurse CRC or licensed independent practitioner with no countersignature requirements.

For more information, see CCR SOP ADCR-13 *Clinical Center External Location Registration and Subsequent Activities*.

6.3 TELEHEALTH VISITS

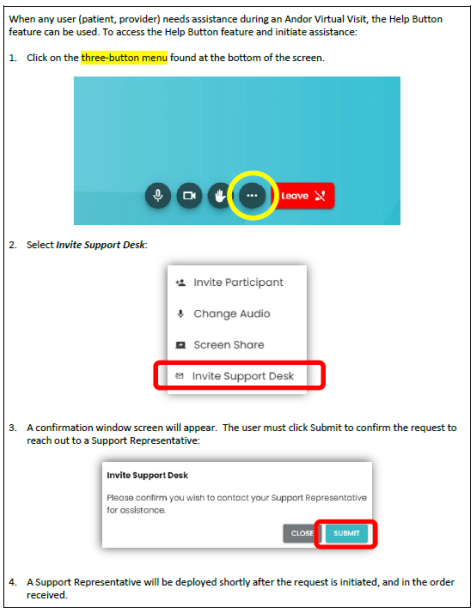
The Clinical Center utilizes ThinkAndor® to support telehealth-related activities. ThinkAndor® is a software platform that provides virtual care experiences to support healthcare. The NIH Clinical Center (CC) offers two components of the ThinkAndor® platform: Virtual Visits (Telehealth) and Virtual Rounding. The Virtual Visits component is the NIH CC's platform that is used for telehealth visits between patients and NIH staff member(s). Virtual Rounding is used to virtually connect NIH staff member(s) with each other (both at the CC or offsite) and/or with research participants who are at the CC to conduct rounds or other 'on demand' types of virtual discussions with patients and/or care teams. For more information about ThinkAndor®, including quick tips, virtual visit and virtual rounding user guides, click here.

Patients are required to complete the NIH-2984 Consent-Authorization for Electronic Communications prior to engaging in telehealth visits with their NIH care provider. All guidelines for the NIH Clinical Center telehealth program can be found in MAS policy M20-1.

Telehealth may be used for clinical purposes when appropriate and incidental to research or research visits. Telehealth visits may occur for new and existing outpatients or for current inpatients when either a patient is unable to travel to the Clinical Center or a provider is working remotely.

If there are any technical difficulties during the telehealth visit:

- Staff may contact the telehealth concierge service at 855-644-6445
  or
- Any user (patient, provider) may select “Invite Support Desk” under the three-button menu at the bottom of the screen to initiate a request with a Support Representative


When any user (patient, provider) needs assistance during an Andor Virtual Visit, the Help Button feature can be used. To access the Help Button feature and initiate assistance:

1. Click on the three-button menu found at the bottom of the screen.

2. Select *Invite Support Desk*:

3. A confirmation window screen will appear. The user must click Submit to confirm the request to reach out to a Support Representative:

4. A Support Representative will be deployed shortly after the request is initiated, and in the order received.

It is mandatory that all telehealth visits be documented in CRIS following the visit. The CRIS templates that are normally utilized when documenting an onsite visit, may be utilized for telehealth visits. If a patient is new to NIH, they should be registered as an External Location (EXT LOC) patient, but unlike the EXT LOC patients who are only submitting specimens or having radiology reads, the Outpatient First Registration note should be entered into CRIS to satisfy their initial visit documentation. Since the full physical examination requirement of this note cannot be completed via telehealth, the clinician shall document an abbreviated exam to the extent possible. Outpatient First Registration notes documented on telehealth patients will automatically have an abbreviated physical exam section present for completion. The completion of a full physical exam will need to be done and documented once and if the patient comes to the Clinical Center for an in-person encounter. Telehealth notes must indicate that the visit was conducted as a telehealth visit. Documentation must be completed by the end of the day on the day of the visit. The Health Information Management Department reviews documentation to ensure it is completed.

6.4 CCR PATIENT REGISTRATION AND ENROLLMENT SYSTEM (PRES).

Research participants who sign an NIH informed consent document are considered enrolled in that clinical research study when both the participant and the Investigator have signed the consent document. Participant registration and status update is completed via the CCR’s Patient Registration and Enrollment System (PRES). Registration is to be completed within 2 business days of the participant signing the consent document.

All participant re-consent, off treatment and off study events are also entered in PRES.

Please see CCR SOP ADCR-2 *CCR Participant Registration & Status Update* and PRES User Guide for details.

6.5 PROTRAK QUERY SYSTEM (PQS)

The Clinical Center's PROTRAK Query System (PQS) is a system for PIs/research teams to enter study-related information to meet the mandatory reporting requirements for clinicaltrials.gov trial registration, federal reporting requirements and to complete the Protocol Reimbursement Impact Assessment (PRIA) review process.

It is maintained by the Protocol Services Section (PSS) and updates are made via the Protocol Support Office (PSO). PQS populates other CC systems including Clinical Center Search the Studies, CRIS and Biomedical Translational Research Information System (BTRIS). The system feeds nightly to clinicaltrials.gov.

6.6 SISWEB

Surgeries, Interventional Radiology procedures, or any other procedures that require anesthesia or anesthesia stand-by, must be scheduled in SISWeb, the online surgery/procedures scheduling system. SISWeb users must be credentialed and have CRIS access.

To Request SISWeb Training:

- Call 301-496-5646 (Monday-Friday 7a-3p).
- SISWeb Training takes only 10-15 minutes.
- Users must be NIH credentialed with CRIS access.

To Obtain Access to POIS/SISWeb:

- Complete and submit the POIS Account Request Form – supervisor's signature is required on the form. The form, SISWeb FAQs and other general information can be found on the Department of Perioperative Medicine website.
- You can also obtain a paper copy from Department of Perioperative Medicine (DPM) Scheduler office/DPM front desk.

6.7 APPROVAL FOR OUTSIDE MEDICAL SERVICES (AOMS)

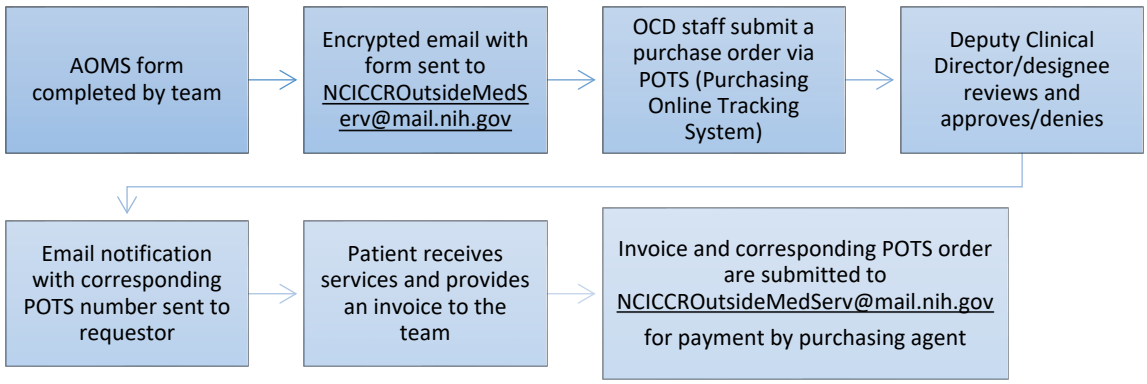
If research procedures/required medical services cannot be conducted at the NIH Clinical Center and are available at an outside facility, these research procedures/medical services may be paid by the NCI Center for Cancer Research. Approval of payment must be secured ***prior*** to the services being rendered to the participant. Staff members should never obligate/promise funds on behalf of the government without an approved purchase order. The CCR cannot

reimburse a patient for costs they've incurred out of pocket. Any requests that may result in a bill over $10, 000 requires additional, advance notice and documentation.

The patient can't proceed with the test or service until:

- The research team completes a request via the Authorization for Payment for Medical Services Outside the Clinical Center form. Please see CCR SOP ADCR-14 *Authorization of Outside Medical Services (AOMS) for Research Participants* for details.
- The request goes to the OCD staff to enter into Purchasing Online Tracking System (POTS).
- That POTS order is routed to Deputy Clinical Director (or designee), to sign off. That sign off means that the government has authorized payment for the test/service.
- Only after signature can the test/service take place.

The turnaround time for this is very quick, but research teams still need to plan ahead. Below is a depiction of the Process for submission of an AOMS request:



Research teams may track the progress of their AOMS requests via OneNote.

Reminders:

- For invoices:
  - Purchasing does not accept copies of MyChart balances as a valid bill/invoice.
  - All invoices must clearly include the participant's name, account number, guarantor number (when applicable), and bill payment information.
    - This information much match the original request form with an accurate date of birth.
  - The preferred format is PDF. Any scanned or faxed invoices must be legible and complete.
  - Check all charges to ensure that what is being submitted are services directly related to the originally approved request.

- If a pre-payment is required for a patient to receive a good/service, our office needs to be notified with a minimum of three business days' notice. Emergency same day orders must be placed before noon.
    - The purchasing agent will require all pieces of information that the vendor will need to process the payment, including a direct billing contact. This typically includes the date and time of the scheduled appointment, a copy of the expected charges, and all applicable account information.
- Please always use @NCICCROutsideMedServ when submitting requests, invoices or other inquiries related to this process.
    - If you have issues encrypting emails to this distribution list, you can expand the list (+ at the beginning of the list name) and it will go through.
- Requests must include a detailed description of services and rationale.
- If there is the potential that a service/procedure will be billed by both the provider and the facility separately, two requests need to be placed. We can't process two bills with different vendors under the same POTS order.
- There is a 90 day follow up on open orders – an invoice or an update is required

6.8 SAFETY TRACKING AND REPORTING SYSTEM (STARS)

The Clinical Center's Safety Tracking and Reporting System (STARS) is for reporting patient safety issues including errors, falls, equipment issues, near misses, etc. that occur in the Clinical Center. It is also a way to give kudos or accolades for staff members. There is an option to submit anonymously.

Any staff may use the STARS system to report patient safety and/or protocol compliance related events (such as PKs or vital signs completed late or not done) to the Clinical Center so they can track and address any issues.
STARS reporting does not replace any required reporting to the IRB, Sponsor or FDA, though it can be part of a corrective or preventative action. When a STARS is placed, it will be routed to the appropriate manager depending on the location and/or nature of the event, and the person who submitted the event can track the progress/resolution on the STARS website.

6.9 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Read CCR SOP ADCR-5 *Travel and Lodging Reimbursement for CCR Clinical Research Participants, Pediatric Guardians, and Authorized Attendants*
2. Review your protocol(s) in PROTRAK/PQS, including the most recent patient travel form
3. Review ThinkAndor® resources (NIH login required)
4. Read CCR SOP ADCR-14 *Authorization of Outside Medical Services (AOMS) for Research Participants*
5. Review CC Safety Tracking and Reporting System (STARS)
6. Read CCR SOP ADCR-2 *CCR Participant Registration & Status Updates*

7. View the PRES training video

7 OVERVIEW OF CLINICAL RESEARCH

7.1 HISTORICAL BACKGROUND

Evidence of clinical studies can be dated back to ancient Chinese medicine. In 15th century BC, early Judeo-Christian and Eastern civilizations document the early origins of clinical research. The Book of Daniel describes a protocol comparing young servants who were given vegetables verses "rich food" for ten days. It was then Hippocrates, around 400 BC, who created high moral standards that have been transposed into an oath taken by medical students which is now embedded in the foundation of a PI's duty. While the case records that have been kept by these minds are used more as a natural history research, we can fast-forward to the 18th century and look at the study of scurvy treatment in the British Navy that was carried out by James Lind. It was one of the first documented records of the modern clinical trial that is seen today. Lind's study was later followed by Edward Jenner's observations that dairymaids did not contract smallpox. Jenner's research introduced the world to vaccinations. It was also during the 18th century that blinded studies were introduced with literal blindfolds to determine if subjects could feel the force of magnetism. Also, in this century was a landmark lawsuit that was filed for surgeons intervening in a patient's fracture without consent, setting the precedent that a physician needs to get informed consent from a patient before performing a procedure. So began the discovery of the global shortcomings relating to protecting human subjects while they are taking part in a clinical trial.

7.2 SELECTED MILESTONES IN THE HISTORY OF PROTECTING RESEARCH PARTICIPANTS

The human experimentation in Nazi Germany led to the Nuremberg Code in 1947. The code outlined 10 ethical principles for clinical research including that one's participation was voluntary, that the benefits of the research outweighed the risks, research participants need to be protected from harm and that they were free to stop participation. In 1953, the NIH opened the Clinical Center and required a medical committee to review all research conducted on human subjects before a study was opened by issuing *Guiding Principles in Medical Research Involving Humans.* In 1962, the Kefauver-Harris Amendment to the Food, Drug and Cosmetic Act required that research subjects be told if a drug was being used for investigational purposes and that consent must be obtained from each research participant. In 1964, the Declaration of Helsinki was adopted by the World Medical Assembly and built upon the Nuremberg Code including preliminary experiments on animals were needed prior to human testing and recommended formation of safety committees.

When light was shed on the U. S. Public Health Service Tuskegee syphilis experiments in African American men from 1932-1972, the Hepatitis B studies at Willowbrook conducted in children

with Down's Syndrome in the mid-1950s, and the 1966 article by Dr. Henry Knowles Beecher describing 22 examples of unethical research conduct in the U.S., research was put into further scrutiny. Congregational hearings on the Quality of Health Care and Human Experimentation were held in 1973 with the consensus that federal oversight was required to protect the rights and welfare of research participants. The National Research Act of 1974 established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and codified DHHS Policies as 45 CFR Part 46 Subpart A. The National Commission released a report in 1979 entitled *Ethical Principles and Guidelines for Research Involving Human Subjects* which became known as The Belmont Report, named for the conference center where the Commission met. The Belmont Report pointed out the differences between medical practice and medical research and identified three basic ethical principles to guide researchers to provide safer medical research. The table below outlines the principles and how they are applied in clinical research.

Principle	**Application**

Respect for Persons
• Individuals are autonomous agents.
• Individuals should be treated with respect
• Persons with diminished autonomy need additional protection.
	Informed Consent
	• Participants must be given the opportunity to choose what shall or shall not happen to them
	• The consent process must include three elements:
	  • Information sharing
	  • Comprehension
	  • Voluntary participation

Beneficence • Human participants should not be harmed. • Research should maximize possible benefits and minimize possible risks.	Assessment of risks and benefits by investigator and IRB
Justice • The benefits and burdens of research must be distributed fairly.	Selection of participants: • Fair procedures and outcomes in the selectin of research participants • Eligibility criteria should include those who may benefit and exclude those who may be harmed

This small historical snapshot has shown that, when left to their own devices, researchers may not conduct their research in an appropriate manner. Regulations and guidelines have been established over time to ensure history does not repeat itself and research participants are protected.

7.3 REGULATIONS & GUIDELINES GOVERNING CLINICAL RESEARCH

It is important for all individuals involved in clinical research to have knowledge and understanding of clinical research-related laws and regulations. Past wrongdoings in the treatment of research participants have led to the development of legal and regulatory systems that scrutinize every aspect of clinical research. Everyone associated with research on humans, regardless of their role, is expected to comply with the laws and regulations that govern the conduct of clinical research practices. It is important to note that regulations, guidance documents, and standards for conducting research are not stagnant; they are living documents that change and evolve. The regulations and guidance documents that impact the conduct of clinical trials are designed to protect human subjects participating in clinical research and ensure the accuracy of the data being collected.

Good clinical practice (GCP) in conducting research refers to a standard that ensures ethical and scientific quality in human subject research. GCP includes laws and regulations as well as internationally recognized standards that must be observed to ensure study quality. Adherence to the principles of good clinical practices (GCPs), including adequate human subject protection (HSP) is universally recognized as a critical requirement to the conduct of research involving human subjects.

To learn about laws, regulations and guidances, please refer to the *Good Clinical Practice (GCP) and Human Subjects Protection (HSP)* online learning module.

7.4 TYPES OF CLINICAL RESEARCH

Clinical research is research on human beings with the goal of generating useful knowledge about health and illness. Clinical research is important because it:

- Improves our understanding of human physiology and pathophysiology
- Translates basic research into medical care
- Informs and drives basic research
- Improves diagnostic tools and preventive care
- Improves human health

Clinical research can be divided into observational research and experimental research. Observational research includes both descriptive (e.g., case reports, series of cases, cross-sectional studies, surveys) and explanatory (e.g., case-control, cohort, natural history) studies. Experimental research includes clinical trials and meta-analysis. The clinical research conducted in the CCR consists mainly of early phase clinical trials, natural history studies and cohort studies (e.g., tissue collection).

To learn more about clinical trials, key concepts and terminology and the phases of clinical trials, please refer to the *Clinical Trial Design* online learning module.

7.5 RESEARCH INTEGRITY

Research integrity means conducting research in such a way that allows others to have confidence and trust in the methods and the findings of the research. Research integrity includes:

- the use of honest and verifiable methods in proposing, performing, and evaluating research
- reporting research results with particular attention to adherence to rules, regulations, guidelines, and
- following commonly accepted professional codes or norms.

Research integrity matters because:

- Researchers rely on trustworthy results of other researchers to make scientific progress
- Researchers rely on public support, whether through public investments or their voluntary participation in experiments, to further science
- The public relies on scientific progress to better the lives of everyone
- The public could be harmed by researchers who are dishonest and act without regards to integrity.

7.5.1 RESEARCH MISCONDUCT

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Research misconduct *does not* include honest error or difference of opinion. Let's explore further the definition and examples of research misconduct:

- Fabrication is making up data or results. For example:
  - Not conducting interviews with subjects and creating records of the interview
  - Making up patient visits and inserting that record into the medical chart
  - Recording the results of follow-up visits that never occurred
  - Filling in/projecting uncollected data

- Falsification is manipulating research materials, equipment, or process or changing or omitting data or results such that the research is not accurately representing in the research record. For example:
  - Substitutions of one subject's record or samples for another's
  - Altering eligibility dates, test results etc.
  - Falsifying dates of data collection to conform with protocol
  - Altering patient data to conform to one's hypothesis

- Plagiarism is the appropriation of another person's ideas, processes, result or works without giving credit which includes self-plagiarism. For example, if you copy sections or rephrase sections in a book or journal article and don't provide a citation.

There are other events that occur in research that are not research misconduct but are reportable to the IRB, sponsor, or others at the NIH. For example:

- Failure to report an adverse event to the IRB or sponsor
- Protocol deviation such as entering ineligible subjects
- Administering a trial drug to non-study participant
- Failure to obtain informed consent
- Breach of patient confidentiality
- Using other's PIV or log-in information.

All NIH staff are expected to report observed, apparent, or suspected research misconduct. The NIH follows PHS policies on research misconduct found at 42 CFR Part 93. It is the responsibility of the Agency Intramural Research Integrity Officer (AIRIO) to oversee the resolution of all research misconduct allegations involving intramural research, and to promote research integrity within the NIH Office of Intramural Research (OIR). Our Agency Intramural Research Integrity Officer (AIRIO) is Dr. Kathy Partin.

The Deputy Director for Intramural Research (DDIR) is committed to full and open communication regarding possible research misconduct within the NIH Intramural Research Program. An online form allows for anonymous, electronic reporting of POTENTIAL research misconduct concerns.

If you suspect any research misconduct, consult with your supervisor to see if you should report the suspected misconduct.

7.6 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Read *The Belmont Report*
2. Complete the *Good Clinical Practice (GCP) and Human Subjects Protection (HSP)* online learning module
3. Complete the *Clinical Trial Design* online learning module

7.7 ADDITIONAL RESOURCES

- NIH IRP Policies and Procedures for Research Misconduct Proceedings
- NIH IRP Guide to the Handling of Research Misconduct Allegations
- NIH Office of Research Integrity

8 PROTOCOL DEVELOPMENT & ANCILLARY REVIEWS

The complexity of developing a protocol and the various review processes required depends greatly on the type of clinical study being conducted. Each study or protocol has a lifecycle:

- Pre-IRB approval involves developing the protocol, navigating the protocol through various ancillary reviews and approvals.
- Initial IRB review and approval involves submitting the protocol and all associated documents (e.g., consent[s], advertising materials, all appropriate ancillary review approvals, FDA safe to proceed documentation for IND/IDE) to the IRB for ethical review and approval.
- Post-IRB review involves all other activities the occur once a protocol has been approved by the IRB (e.g., modifications/amendments, continuing review, event report).

This section will focus on the pre-IRB processes including scientific review.

8.1 INITIAL PROTOCOL DEVELOPMENT

The PSO will provide support for the PIs for protocol writing and development. It is important for the PI and research team to understand if the proposed research protocol/study is human subjects research or not. This will then determine how the protocol will be developed and what reviews will be needed. A protocol or research activity involving human subjects research will need IRB review and approval unless an exemption is granted. A protocol or research activity that isn't human subjects research does not need IRB review.

Human subjects research is simply research on humans. Research is defined as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Of note, the FDA uses the term clinical investigation to be synonymous with research and defines clinical investigation as any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA . . . [or] the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. A human subject as defined by the 2018 HHS Common rule (also known as Title 45 Part 46 Subpart A), is a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

The FDA defines a human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Not human subjects research is research not involving a human subject if:

- there is no interaction or intervention with living individual, and
- neither the provider of the specimens/data nor the recipient can link the specimens/data with identifiable individual either living or dead
  OR
- the provider of the specimens/data is not an investigator or collaborator in the research activity, and
- the specimens/data have no code linking them with identifiable individuals, or it would be impossible for the recipient to use the code to identify someone because the provider of the specimens/data is prohibited from releasing identifiers.

If the research is "not human subjects research," a formal determination by OHSRP is not mandatory for research activities involving only use (including secondary use study or analysis) of coded or de-identified (not individually identifiable) of human specimens and/or data. Investigators should assess whether their research meets the regulatory definition of human subjects research. If an investigator is not certain, a request for a formal determination may be made through PROTECT.

To learn more about human subjects research or not human subjects research, see Chapter 1 of the NIH Investigator Manual for Human Subjects Research.

8.1.1 PROTOCOL AND CONSENT TEMPLATES

PIs should use the protocol and consent templates available on the IRBO website.

All protocols will have similar content which includes:

- Recruitment plan
- Plan for screening and enrollment
- Plan detailing how the privacy and confidentiality of research participants will be protected and how the safety of the research data are being ensured both while the research study is being conducted and once it has been completed.
- Description of the research to be conducted
  - Protocol Summary
  - Introduction
  - Objectives and Endpoints
  - Study Design
  - Study Population
  - Study Intervention, if applicable

    - Study Intervention Discontinuation and Participant Discontinuation/Withdrawal
    - Study Assessments and Procedures
    - Statistical Considerations
- Data safety monitoring plan (DSMP) that is commensurate with size, the level of risk and the complexity of the research to monitor the data collected to ensure the safety of subjects
- Explanation of the compensation plan, including the method, timing of distribution, and amount for compensation of research subjects in your protocol and consent forms.
- Detailed description of the consent process and, as applicable, the process for obtaining parental permission and assent, or how consent will be obtained by a subject's legally authorized representative if the subject lacks the capacity to consent to research participation.

There are several protocol templates and forms on the OHSRP website.

- There are two templates to be used for interventional research: the Interventional Drug/Device Trial template and the Behavioral and Social Science Research Template both follow the format of the NIH/FDA template and are ICH GCP compliant.
- There are three templates to be used for observational research: the Natural History/Observational Protocol template, the Repository Protocol template, and the Secondary Research Protocol template.
- There are two templates (and accompanying instructions for each) to be used for exempt research, one for prospective data collection and the second for retrospective data collection/biospecimen review.

None of the templates are likely to be perfect for a given study without some modification. The IRB expects that the PI will adapt the template to suit their needs.

Also, on the IRBO website are several templates for informed consent and assent documents. Visit the website to learn more.

PSO Managers work with PIs to develop the protocol and consent(s)/assent document(s).

For CCR-held IND protocols, OSRO has a template for these sponsored protocols which the PSO will use to assist the PI in writing their protocol.

8.1.2 SECONDARY RESEARCH

Secondary Research is research use of information and biospecimens that were collected through interaction or intervention with living individuals for some other “primary” or “initial” purpose (e.g., a clinical purpose or a different research protocol). In other words, the materials were not collected from humans for the purpose of the specific proposed study.

The use of identifiable specimens or data for new research questions constitutes human subjects research which must be described in a new protocol and IRB approved prior to moving forward. In addition, if the investigator plans to share the existing specimens or data with a collaborator who will conduct analyses and return individual level results that they can link back to subjects to answer these questions, this activity also constitutes human subjects research which must be IRB approved. In these cases, the investigator's activities are considered secondary research. This means that a secondary research protocol must be written and submitted for IRB approval.

If the research team can remove all identifiers and codes from the study database and specimens and destroy the code key (i.e., everything is anonymized). Once the specimens and data have been anonymized, any research activities conducted with these materials would be considered "not human subjects research" and no further IRB oversight would be required.

Reminder: For collaboration with outside researchers, remember that a tech transfer agreement will be needed. See Section 8.4.2 for more information on technology transfer agreements.

You can also direct the investigator to Chapter 1 of the NIH Investigator Manual for Human Subjects Research.

8.2 SCIENTIFIC REVIEW

The scientific review process applies to clinical protocols (e.g., clinical trials, non-interventional natural history studies, screening protocols, and teaching and training protocols). Scientific review includes the initial concept and full protocol review, annual and quadrennial review of the ongoing protocol, and review of substantive modifications to the protocol that pose new scientific questions. Except for concept review, these reviews become a part of the official protocol record and are made available to the IRB, and NIH leadership.

The scientific review must include an assessment of the protocol's resource requirements for the Clinical Center and the Institute/Center (IC) sponsoring the protocol, as well as anticipated service needs provided by other ICs as applicable.

Intramural Research Program (IRP) PIs are responsible for ensuring clinical protocols involving non-exempt human subjects research have undergone review of scientific content, or obtained a waiver, consistent with the *Policy for Scientific Review of Clinical Protocols Utilizing the NIH Intramural Program*. This requirement must be met prior to initiating IRB review.

To learn more about how the scientific review process works in the CCR, review the *CCR Scientific Review SOP*. The CCR scientific review website also has a list of meetings, FAQs, and other resources to help your PI. It is recommended that you join the listserv (i.e., Click here and

send the generated email message) to receive notifications about upcoming meetings. This is one way you can learn what your PI has in the pipeline that may not yet have made it to the team meeting.

8.3 DATA MANAGEMENT AND SHARING (DMS) PLAN

The NIH Data Management and Sharing (DMS) Policy promotes the sharing of scientific data. Sharing scientific data accelerates biomedical research discovery, in part, by enabling validation of research results, providing accessibility to high-value datasets, and promoting data reuse for future research studies.

Under the DMS policy, NIH expects that investigators and institutions:

- Plan and budget for the managing and sharing of data
- Submit a DMS plan for review when applying for funding
- Comply with the approved DMS plan

For the Intramural Research Program, a Data Management and Sharing (DMS) plan will be required for scientific data from research associated with a:

- ZIA (human and non-human research)
- Clinical protocol that will undergo IC Initial Scientific Review
- Genomic Data Sharing (GDS) project

Principal Investigators are required to develop the DMS plan PRIOR to starting the research. For more information about DMS Plans and resources see the following CCR SOPs:

- RPS-22: *Requesting a Data Management and Sharing Waiver*
- RPS 23: *Registering a Clinical Trial in dbGAP*

The single DMS Plan incorporates the requirements of both the DMS and GDS policies.

8.4 ANCILLARY REVIEWS

In addition to the requirement for IRB review for non-exempt (i.e., needs IRB review) human subjects research conducted by NIH investigators, ancillary reviews may also be required. Ancillary reviews include but are not limited to:

- Deputy Ethics Counselor Review
- Office of Technology Transfer Review
- Scientific Review
- Radiation Safety Committee (RSC)
- Institutional Biosafety Committee (IBC)

The PI is required to ensure that necessary ancillary reviews are completed and approved *prior* to initiation of non-exempt human subjects research. However, as the study coordinator, you need to be aware of these review processes as they will impact study implementation.

When an NIH IRB is the Reviewing IRB, documentation of approval by the required NIH ancillary review entities must be provided to the NIH IRB. When the NIH relies upon a non-NIH Reviewing IRB, approvals by NIH ancillary review entities are still required, and documentation of such approval must be provided to the Office of IRB Operations (IRBO) prior to submission to the Reviewing IRB. See HRPP Policy 106 *Ancillary Reviews* for more details.

8.4.1 DEPUTY ETHICS COUNSELOR REVIEW

It is the Federal Government's policy to eliminate or minimize actual or perceived conflict of interest (COI) in the conduct of clinical research, which is intended to promote objectivity and to maintain the public's trust. The NIH requires that actual or apparent COI be considered for all investigators working on a covered research protocol (CRP). CRPs include:

- Studies of investigational drugs and devices
- Studies with a research question about a commercially available drug or device, and
- Studies involving collaborations with a substantially affected organization (SAO) or another for-profit entity when the entity is receiving data or specimens from the NIH for the purpose of developing a product.

Most interventional protocols will be CRPs unless the intervention does not involve the criteria listed above (e.g., a behavioral intervention might not meet the criteria for a covered research protocol or use of a device for physiological exploration where there is no intent to develop a commercial application).

To explain these requirements, all investigators working on a CRP must be provided the COI Guide which will be provided by your team's PSO manager. In addition, the names of all investigators working on a CRP must be submitted to the IC Deputy Ethics Counselor at specified time points (i.e., initial review, continuing review, adding a new investigator), via PROTECT. This will be done by the PSO manager. Once the IC DEC has completed the review of the protocol, the COI outcome letter is uploaded in PROTECT by the PSO manager assuring the IRB that NIH COI requirements have been met.

Investigators are required to complete one of two forms:

- Federal employees complete the *Confidential Report of Financial Interests in Substantially Affected Organizations for Employees of the NIH* form which is often just referred to as form 717-1. A member of the NCI's Ethics Office will send instructions.

- Contractors follow their employer's COI policy. Then for each protocol they are designated as an Investigator, they will need to complete the *Conflict of Interest (COI) Certification for Non-Federal Employees* form sent by the team's PSO manager.

8.4.2 OFFICE OF TECHNOLOGY TRANSFER REVIEW

Technology Transfer is the process of transferring knowledge and/or materials from one organization to another to promote the further development and commercialization of technology. Activities may include:

- Sharing materials and information
- Protecting technologies through patents (NIH does not copyright work of NIH employees)
- Licensing technologies to further develop and commercialize the technologies
- Developing partnerships and collaborations to advance scientific research and development
- Partnering with academic, industrial, and economic development organizations to foster economic growth

The NIH Office of Technology Transfer (OTT) plays a strategic role by supporting the patenting and licensing efforts of our NIH ICs. OTT protects, monitors, markets, and manages the wide range of NIH discoveries, inventions, and other intellectual property as mandated by the Federal Technology Transfer Act and related legislation. To accomplish its mission, OTT staff provide management and oversight of the collection and disbursement of royalties, monitor, and enforce patent rights and licensing agreements, coordinate the payment of all patent annuities, market available technologies to the private sector, provide legal docketing services, and provide technology development systems support and expertise to the NIH Technology Transfer community. The OTT has numerous templates for the various forms and model agreements that are used. Each IC has their own office. For NCI, this is the NCI Technology Transfer Center (TCC).

Technology transfer is a team effort and involves:

- CCR Scientists/Investigators who conduct cancer research
- NCI Technology Transfer Center (TTC) where staff:
    - Evaluate inventions and manage invention reporting.
    - Work with scientists to select best agreement type; negotiate agreements
    - Match NCI discoveries with partners, and facilitate collaborations
    - Manage patenting through contract law firms
    - Manage licensing via NIH licensing specialists
    - Manage license monitoring, auditing and enforcement.
- Other NIH Offices
    - Office of Budget and Finance

- Office of General Counsel
- Office of Human Subjects Research Protections
- NCI Ethics

The types of agreements are found in the table below:

Type of Agreement	**Description**

Confidential Disclosure Agreement (CDA)	• Protects the exchange of confidential information between two or more parties
	  ○ CRADA discussions/negotiations
	  ○ Discussing unpublished data
	  ○ Patent filing
	  ○ Grant submissions

Material Transfer Agreement (MTA)	• Send and receive research materials • Frequently used in academic collaborations • NOT FOR USE IN HUMANS • No further distribution
Clinical Trial Agreement (CTA)	• Receive investigational drug for the conduct of clinical trials
Collaboration Agreements	• Joint research project with universities, non-profit organizations or industry
Cooperative Research and Development Agreements (CRADAs)	• Collaborative research project, often with industry • NCI can receive funds but not provide funds directly to CRADA collaborator • Provides a license option to the collaborator

Based on the type of agreement, there will be different levels of leadership that need to sign the agreement. For example, the CCR Director signs off on any CTA but for a CRADA, the NCI Director signs off and clearance from Ethics and NIH are needed. When all parties have signed the agreement, the agreement is considered "executed." Below are the NCI TTC Timing Goals for executing an agreement:

- MTAs and CDAs: 1 – 2 Weeks
- Collaboration Agreements: 1 – 2 Months
- CTAs: 1 – 3 Months
- CRADAs: 1 - 6 Months

For more information, please view the CCR Clinical Research Forum from October 25, 2023 titled "Technology Transfer Agreements."

8.4.3 RADIATION SAFETY REVIEW

Approval by the Radiation Safety Committee (RSC) is required before the initiation of clinical research studies involving the use of the following:

- Radioactive research drug(s) regulated under the FDA requirements for review by the Radioactive Drug Research Committee (RDRC)
- The use of any radiation in pediatric participants (<18 years old) with an annual effective dose > 0.5 rem or healthy pediatric volunteers (any dose level)
- Any radiation in healthy adult volunteers, excluding DEXA and chest X-ray
- Therapeutic administration of radioactive materials, novel uses of radiation, including any radioactive Investigational New Drugs (IND) and radiation-producing investigational device
- The radiation itself is the research agent being studied

The RSC meets monthly. An RSC submission is created in PROTECT by the PI or PI Proxy (e.g., PSO Manager). All communication to and from the RSC is managed in PROTECT.

During the development of the protocol, PSO managers work with the PIs to incorporate the appropriate protocol language and to navigate the protocol through the radiation safety review and approval process which occurs prior to submitting the initial protocol to the IRB. However, all study team members should be aware of when RSC approval is required and when RSC review is approved.

8.4.4 INSTITUTIONAL BIOSAFETY COMMITTEE REVIEW

The Institutional Biosafety Committee (IBC) is an advisory body to the Division of Occupational Health and Safety (DOHS), Office of Research Services (ORS). This committee reviews basic and clinical research involving recombinant Deoxyribonucleic Acid (DNA), including human gene transfer, or potentially infectious/toxic materials to ensure that proper containment and biosafety practices are employed. This committee provides recommendations to the Director of the NIH or his designee, and the Deputy Director of Intramural Research (DDIR) reviews all infectious disease research performed at BSL-2 and above and any research that falls under the *NIH Guidelines for Research involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines).

All Principal Investigators (PIs) working with human, plant, or animal pathogens must register their work with the Institutional Biosafety Committee (IBC). This is done through the DOHS electronic biological registration interface (i.e., the PI Dashboard), which can be accessed through the DOHS Principal Investigators resource page. PIs may consult with IBC contacts, Institute assigned safety specialists, or a Biological Safety Officer, BSO through DOHS at 301-496-2960 if they will be conducting basic and/or clinical research involving recombinant DNA, including human gene transfer, or potentially infectious/toxic materials to ensure that proper containment and biosafety practices are employed. PSO Managers will work with the PIs to

ensure that applicable protocols are submitted in the relevant electronic review system and be reviewed by the NIH IBC.

8.5 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Federal employees: Complete the HHS Form 717-1 form.
2. Contract employees: Complete the *Conflict of Interest (COI) Certification for Non-Federal Employees* form sent by the PSO for each protocol you are listed as an investigator on.
3. Review the *CCR Scientific Review SOP*
4. All Investigators: Complete Technology Transfer training. Log into the LMS home page. Search for the NIH Online Technology Transfer course which should have a "current" box next to the version.

8.6 ADDITIONAL RESOURCES

- NIH Investigator Manual for Human Subjects Research
- IRBO website *Conflict of Interest Review by IC Deputy Ethics Counselors (DECs)*
- HRPP Policy 102 *Investigator Conflict of Interest and Government Royalties*
- IRBO website *NIH Radiation Safety Committee (RSC)/ Radioactive Drug Research Committee (RDRC)*
- NIH Radiation Safety Committee website
- Radiation Dose Library for Common Procedures website

9 INSTITUTIONAL REVIEW BOARD

The Institutional Review Board (IRB) is an administrative body that provides ethical review of protocols to ensure that human subjects rights and safety are upheld and maintained under applicable federal regulations and institutional policies (Office of Institutional Review Board (IRB) Operations).

Research team members, especially PIs and CRCs, are responsible for knowing which IRB is responsible for each of their protocols and what their processes are, including what events to report, how to report them and timeframes/deadlines.

Types of IRBs include:

- NIH IRP
- Advarra/WIRB/Streamlined, Multisite, Accelerated Resources for Trials (SMART)
- NCI CIRB
- Other IRBs based on reliance agreements

To learn more about the role of the IRB, refer to the *Protocol Development, Review and Approval* online learning module.

9.1 ELECTRONIC IRB MANAGEMENT SYSTEM: PROTECT

The **Prot**ocol **E**lectronic **C**apture **T**ool (PROTECT)is the Huron IRB electronic submission system used by the NIH IRP IRB. You may request a PROTECT account using the PROTECT Help Center website. When a new user requests an account, a trainer will reach out to you to follow up and ensure you are signed up for an upcoming training. This site also offers topic specific PROTECT Training and User Guides and the PROTECT Training Instance, a helpful resource to practice using the system.

9.2 INITIAL REVIEW

9.2.1 PRE-REVIEW

Before a protocol is reviewed by the IRB, one of the IRB Analysts will review the submission to make sure that the submission package is complete. They may send a request for Pre-review Clarifications in PROTECT asking for additional information or corrections to the submission. The goal of this process is to address any potential barriers that may cause delays in approval before the protocol is reviewed by the IRB.

9.2.2 TYPES OF IRB REVIEWS

There are two types of IRB reviews: Expedited Review and Full Board.

- Expedited review: review of research that falls within one of nine specific categories and that is reviewed by an IRB Chair or a designated reviewer. If the protocol is eligible for expedited review, an IRB Chair or an IRB Chair Designee will review the protocol for approval. The period of approval begins on the day protocol was approved by the designated expedited reviewer and continues until the date the study is closed or through a specified date according to Continuing Review (CR) requirements.
- Full Board IRB review: the protocol must be reviewed by a fully convened IRB to receive approval. The protocol will be assigned a meeting date that can be viewed in electronic IRB system.

9.2.3 IRB DETERMINATIONS

There are 2 possible IRB Determinations after Expedited Review of the protocol:

- Approval: The Expedited Reviewer has determined that the protocol has met the criteria for IRB approval of research. Please see the next chapter for additional actions that must take place before starting enrollment after IRB approval.
- Modifications Required to Secure Approval: The Expedited Reviewer has determined that the initial review submission needs modification to meet the criteria for IRB approval of research. This may include changes to the protocol/consent; the submission

of additional information; or additional actions that need to take place before the protocol can be reconsidered for approval. The Expedited Reviewer will work with the research team to ensure that the protocol meets all approval criteria.

During the expedited review process, it is always possible that additional information may be discovered that requires the protocol be referred for review by the Full Board. The reason for this change should be communicated to the PI by the Expedited Reviewer or IRB Analyst. There are 4 possible IRB Determinations after Full Board Review of the protocol:

- Approval: The IRB has determined that the protocol has met the criteria for IRB approval of research.
- Modifications Required to Secure Approval: The IRB has determined that the protocol has met the criteria for IRB approval of research; however, this is dependent on the acceptance of changes required by the IRB. This option is used when the IRB is able to provide specific necessary changes that avoids deferral of the submission and delayed IRB approval.
- Deferred: The convened IRB is unable to determine that the criteria for IRB approval have been met. The IRB will require substantive modifications to the submission that may include changes to the protocol/consent; the submission of additional information; and/or additional actions that need to take place before the protocol can be reconsidered for approval. The changes will require review by the Full Board.
- Disapproved: The IRB has determined that the protocol does not meet the criteria for IRB approval of research. The research team will have to submit a new initial review submission if this occurs.

9.3 RELIANCE AGREEMENTS

The revised common rule of 2018 (i.e., 45 CFR 46.114[b]), requires at that all institutions located in the United States that are engaged in multi-site or cooperative research conducted or supported by a Federal department or agency rely upon approval by a single IRB (sIRB) for the portion of the research that is conducted in the United States.

The NIH single IRB policy came into effect on January 25, 2018. The goal of the Policy is to streamline the review of multi-site research without compromising protections. It requires that all domestic sites of NIH-funded multi-site studies use an sIRB to review nonexempt human subjects research under the applicable regulations (45 CFR 46 and 21 CFR 56). Multi-site studies are those that use the same protocol to conduct non-exempt human subjects research at more than one site and the Policy applies no matter the extent to which an individual site is involved in the protocol's research activities. The sIRB Policy applies to multi-site studies that receive any funding from the NIH.

The Policy does not apply to foreign sites, nor career development, research training or fellowship awards. For more information about sIRB at NIH, please refer to *The Single IRB Model at the NIH: Principles, Processes, and Pitfalls.*

A Reliance Agreement is a written agreement between institutions that identifies which institution will serve as the Reviewing IRB and which will cede IRB review i.e., the Relying Institution. It outlines the respective roles and responsibilities and is negotiated by the respective Human Research Protection Programs.

Reliance Agreements can document NIH relying on an external IRB, or an external institution relying on the NIH IRB. PSO managers can initiate a request for a Reliance Agreement by submitting a reliance request in the NIH reliance system if NIH needs to rely on an external IRB, or if research teams want to request for an external site(s) to rely on the NIH IRB.

The IRBO website for Reliance and Single IRB Resources contains information on getting started, OHSRP Education series presentations, and agreement requests. There are two important guidelines which outline the requirements for considering reliance requests:

- *Guidelines for NIH Study Teams Planning To Submit New Multi-Site Protocols In Protect And Want The NIH To Serve As The Reviewing IRB For The External Participating Sites*
- *Guidelines For NIH Study Teams Wanting to Rely on an External IRB (Does Not Apply To Submissions to the NCI CIRB)*

The NIH IRP has a program wide reliance agreement with WCG IRB, Inc., Advarra, and NCI CIRB and a master reliance agreement with Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB.

Even when relying on another IRB (i.e., the NIH IRB ceded to another IRB), an NIH Institutional review is still required. This review ensures that NIH is operating according to the terms of its Federalwide Assurance (FWA) and that all NIH institutional requirements are met before NIH relies on an external IRB. It is carried out by NIH IRBO but is a different type of review to the ethical and regulatory review undertaken by the external IRB; it is an administrative review, not an IRB review.

This review typically occurs before NIH is added as a site to a multi-site protocol being reviewed by an external IRB. What this means is even if the IRB of record has approved the protocol and our local consent, the NIH Institutional Review still needs to occur before research teams can move forward with the protocol or even a modification. The PSO manager will initiate the process via PROTECT.

9.4 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Request PROTECT account, attend training class

2. Complete the *Protocol Development, Review and Approval* online learning module

10 POST INITIAL IRB APPROVAL

Once the protocol has been approved by the IRB, there are other activities that need to be completed prior to enrolling participants including protocol training and study initiation activities. Through the lifespan of the protocol, there are various regulatory reviews that occur and mandatory results reporting until study closure.

10.1 PROTOCOL TRAINING

The PI is responsible for ensuring that all study staff working on a research protocol are adequately trained on the protocol, including informed consent and other applicable protocol documents (e.g., Investigator Brochure, manuals, etc.) as required depending on their role in the study. All study staff listed on the delegation log must have protocol training and the training must be documented. Training must take place prior to, or on, staff "start" date on the delegation log.

CCR SOP PM-5, *Research Protocol Training Requirements*, provides procedures for team protocol training and documentation. Documentation of the training will be maintained in the regulatory file.

10.2 STUDY INITIATION ACTIVITIES

The PI is responsible for ensuring that all applicable protocol initiation activities are completed before a new clinical research study opens to participant recruitment. This is to ensure that the appropriate protocol infrastructure is in place and coordinating departments are aligned prior to enrolling participants. Completion of these activities is critical for ensuring a smooth study start that maintains protocol and data integrity while protecting research participants. The CRC works with the PI to coordinate, complete and track these activities.

CCR SOP PM-7, *Study Initiation Activities*, outlines all activities that must be completed before opening to recruitment. This includes a fillable checklist that is signed by the PI once all applicable activities are completed. The signed checklist is then forwarded to the team's PSO Manager, who will change the study accrual status in the PQS-PROTRAK Query System. Once that happens, PSS will then post the consent, and activate the protocol in CRIS so that protocol order sets will be available, and the research team will be able to assign orders to that protocol.

10.3 MODIFICATIONS

Modifications are changes to any part of the study including:

- Protocol
- Consent
- Investigator Brochure (IB)
- Updated package inserts
- Study team member changes

These must be reviewed and approved by the IRB prior to implementation.

10.3.1 MODIFICATION TRAINING

The PI is responsible for ensuring that all study staff are updated when a protocol modification is approved by the IRB. This update can be done via team meeting, separate training meeting or email notification, depending on what changes were made during the amendment and how the amendment impacts the staff role based on their responsibilities on the study.

CCR SOP PM-9, *Research Team Training Requirements for IRB Modifications,* provides procedures for team protocol training and documentation. Documentation of the training will be maintained in the regulatory file.

10.4 CONTINUING REVIEW (CR)

The purpose of a continuing review (CR) is for the IRB to evaluate a clinical research study on an ongoing basis for any new information and study progress that may affect research participant safety, risks, benefits, and/or willingness to enroll. The frequency of the CR is at least annually but may be more frequently for higher risk studies. This is determined by the IRB and the expiration date will be noted in the NIH IRB Approval memo. Of note, some research studies will not need a CR but rather a progress report. A progress report is for minimal risk studies and contains fewer questions than a CR. It is important for the CRC to know the IRB approval expiration date of each study they are coordinating. Setting an Outlook reminder is helpful.

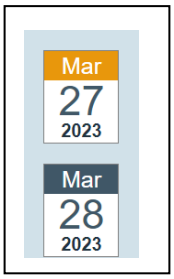
Human Subjects Protection Program (HRPP) policies to be familiar with include:

- Policy 104 – Research-Related Subject Complaints
- Policy 204 – Levels of IRB Review and Criteria for IRB
- Policy 801 – Reporting Research Events

When IRB approval lapses for a study, all research activity must cease, except for activities necessary to ensure the safety of research participants, but permission from the IRB Chair must be obtained. Lapses in IRB approval are disruptive to the research and place the investigator and institution at regulatory risk. If there is a lapse in study approval, the IRB will not review any new studies submitted by the PI until the CR has been submitted or the study has been closed. If 45 days after study expiration, no CR application or study closure has been submitted in PROTECT, the IRB will administratively close the protocol. Continued research will require submission of a new protocol to the IRB.

10.4.1 CR NOTIFICATION PROCESS AND INFORMATION SUBMITTED

The research team will receive CR reminders from PROTECT. The PROTECT dashboard will also show studies that are expiring soon in the left-hand corner. They are color coded on the month name as follows:



- Blue: Expiration date is between 60 and 15 days away
- Orange: Expiration date is 15 days or less before the expiration date
- Red: day of expiration or it is within 6 days after the expiration date

The color coding will disappear once 6 days have passed since the expiration date.

The CR application is due to the IRB via PROTECT 30 days ahead of the study expiration date. PROTECT will generate and send reminder emails to the research team and PSO manager about upcoming CR deadlines.

The CR application consists of a form in PROTECT on which the researcher records any changes, incidents or other problems that have occurred since the study was approved, or since the previous continuing review. The PSO manager will send the PI and CRC an email with the questions, the data cut-off date, and a due date for the research team (ahead of the IRB deadline) to return the requested information.

The PI and CRC will work together to answer the requested questions and write the high-level summary. Note that all information should be updated as of the cut-off date. Do not include any information obtained after the cut-off date without an explanation as to why. For treatment studies, the progress/findings section should include at a minimum the number of patients enrolled, treated and disease responses since the study started and the last continuing review.

The research team will receive an NIH IRB Approval memo from PROTECT via email once the CR has been reviewed with approval status and stipulations to address, if applicable. These should all be saved to the regulatory file.

10.5 FDA ANNUAL REPORT

FDA Annual Reports are submitted yearly to the FDA to provide a status update on each investigational new drug (IND). For CCR-held INDs, a representative from the Office of Sponsor and Regulatory Oversight (OSRO) will email the PI with the required content a few weeks in advance of the due date, including adverse events and demographics tables. Please reference IND Annual Reports – Data Reporting Process and Logic for information regarding the table format. Please note that the same IND may be used for multiple protocols across different

teams and branches. The PI is only responsible for the content for their own protocols. The OSRO IND team will compile the rest.

The CRC and data manager will work together to ensure enrollment, eligibility, study medication administration, off treatment, off study and adverse events eCRFs are complete and accurate as of the data cut-off date. The PI and CRC work together to answer the rest of the questions about toxicities, off study reasons, results, the investigational plan for the upcoming year, manufacturing changes, publications, etc. It is helpful to reference the last FDA Annual Report to maintain consistency. If it is a gene or cell therapy protocol that requires long term follow up from the FDA, PIs may be asked to provide additional information about replication competent retrovirus (RCR) blood results and patient status including death dates.

The process for FDA Annual Reports is different for outside sponsor-held INDs. The sponsor will compile the FDA Annual Report. The research team's job is to make sure the data in the clinical database is complete. Teams can expect to receive more database queries leading up to the FDA Annual Report due date that will need to be addressed.

10.6 SAFETY MONITORING COMMITTEE AND OSRO DATA AND SAFETY MONITORING BOARD

The Safety Monitoring Committee meets quarterly to review protocols that meet at least one of the following criteria:

- NCI CCR multi-institutional treatment protocols for which the NCI CCR is the coordinating site
    - SMC will not monitor a CTEP-sponsored protocol if this is the only SMC qualifying criteria for the protocol.
- Gene transfer or gene therapy
- Protocols that the CCR believes require special attention due to high public interest or public perception of risk or potential conflict of interest including studies where PI/AI hold a patent
- All protocols that are deemed by the IRB to pose potentially very high risk to patients.

If a Data Safety Monitoring Board (DSMB) or equivalent exists, SMC review may not be needed as per the Clinical Director. If SMC review applies, the PI and CRC will receive an email from The Director of the PSO with the meeting date, data cutoff date and submission deadlines. The CRC and data manager work together to ensure adverse event eCRFs are complete and accurate and pull the specific SMC AE report from the database. The PI and CRC work together to answer the rest of the questions. It is helpful to refer to the last SMC report, if available, to maintain consistency. See CCR SOP PM-15 *Preparation of Safety Monitoring Committee (SMC) Report* for more information.

Some CCR-held IND protocols will be reviewed by OSRO's Data and Safety Monitoring Board (DSMB). Each protocol will state which review, if any, applies. For more information see OSRO DSMB. Click here to learn more about OSRO's DSMB visit including the Policy, Charter and other information.

10.7 STUDY CLOSURE

A protocol cannot be closed with the IRB if any of the following conditions apply:

- Enrollment continues
- Research-related interventions are still being conducted
- Subject follow-up is ongoing
- Biological specimens or data containing personally identifiable information (PII) or linked to PII are being used for research activities described in the protocol (i.e., still be used for analysis)
- Manuscript preparation or responses to requests by the journal prior to publication are not yet complete (These activities may involve the need to access PII about the subjects)
- If the protocol is part of a multi-site study with local IRB review, and the sponsor has not provided permission to close the protocol with the IRB
- If the protocol is part of a multi-site study with single IRB review AND research activities are ongoing at one of the sites OR the sponsor has not provided permission to close the protocol with the IRB.

A protocol should not be kept open to continue analyses to answer new research questions.

If the PI is serving as the lead investigator or the NIH is the Coordinating Center (a multisite study with local IRB oversight at the NIH), the protocol must remain open with the IRB if the NIH is still receiving, studying, using, or analyzing identifiable private information from other sites (even if all interventions, interactions, observations, and data collection at NIH are complete).

Although investigators may feel reluctant to do so, there are times when it is appropriate to close the protocol with the IRB. Per OHSRP Policy 3014-204, once the research team has completed all the procedures described in the protocol, collected all the necessary data and specimens, performed the planned data analysis to meet the research objectives, and published, it is likely time to close. At this point, a modification to the study for study closure will be submitted in PROTECT. When a protocol prematurely ends, is stopped by the PI, or is stopped or closed by an outside sponsor or the IC, the PI must also request study closure. This request serves as notification to the IRB that continuing review of the protocol is no longer needed.

Once a protocol is closed:

- Contact with subjects for research purposes is no longer permitted
- Specimens and data may no longer be collected; and
- No further analysis or other research related activities can occur with identifiable (or coded and linked with access to a code key) specimens and data.

A study closure can be submitted at any time; research staff do not need to wait for the time of continuing review or the end of the research approval period to close a protocol.

10.7.1 STEPS TO CLOSE A STUDY

Under development – for questions contact the Office of Education and Compliance

10.8 REPORTING RESULTS TO CLINICALTRIALS.GOV

All our clinical trials need to have the clinical trial's results reported to clinicaltrials.gov per the 2007 Food and Drug Administration Amendment Act Section 801 and the 2017 NIH Policy on the Dissemination of NIH Funded Clinical Trials Information, and the Final Rule for Clinical Trials Registration and Results Information Reporting. In the CCR, our Program Analyst (PA), Lisa King, provides support for this reporting. All reporting is done through the Protocol Registration and Results System (PRS) and must occur within one year of the protocol primary completion date (PCD). Two definitions are important to understand:

- Responsible Party (RP): the sponsor of the clinical trial (as defined in 21 CFR 50.3) or the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements for the submission of clinical trial information.
- Primary Completion Date (PCD): the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

For more information from the FDA's perspective, watch their three-part webinar series on ClinicalTrials.gov.

10.8.1 REPORTING THE PRIMARY COMPLETION DATE (PCD)

The Responsible Party (i.e., the PI) must report the primary completion date to the Protocol Services Section (PSS) within 30 calendar days after the clinical trial reaches its actual primary completion date using the PQS-PROTRAK Query System. If the study has two primary outcome

measures (e.g., phase I/II study), report the PCD when the second primary outcome reaches the primary completion date.

CRCs should track the PCD for each study. Begin by looking at the primary objective(s) and determine how this is being measured. This would include a procedure and a timeframe. The table below provides some examples.

Primary Objective/Outcome	Timeframe
To determine the safety and tolerability	Date the last participant had the safety visit. This could be 28, 30 or 90 days and is typically noted in the study calendar and/or the off-treatment section of the protocol.
To determine Best Overall Response (BOR) (PR+CR) according to Response Evaluation Criteria (RECIST v1.1)	Date of the last participant's imaging study
To determine the MTD	Date the last patient was evaluated for a DLT so you will need to know the DLT window. This is found in the DLT subsection of a protocol. Typically this is one cycles, but may be two or another timepoint.

It is important to keep the anticipated primary completion date updated. At the time of CR, the PSO Manager will ask the research team to confirm the date and update as needed.

10.8.2 PI NOTIFICATION

The CCR's Program Analyst, Lisa King, will email the PI, Research Team, and/or ORN Team Lead and:

- Inform the PI results reporting will begin for the clinical trial
- Provide the results submission deadline
- Ask the PI for the last IRB approved protocol, consent, and/or any publications and data for the clinical trial; inquire if protocol and/or consent need to be redacted.
- Inform the PI data management will create reports (i.e., FDAAA reports) from their data on one of the CCR clinical databases (e.g., C3D, RAVE, LabMatrix)
- Provide one-on-one or group sessions for results reporting
- Provide contact information for questions

The Director of the Protocol Services Section (PSS) will email the PI and inform them of:

- Results submission deadline and consequence for failure to report on time
- Transfer of ownership of the record to the PI as the RP and that access to PRS given to Protocol Analyst
    - PI will be given a username and password for the CT.gov database when ownership is transferred to the PI for a protocol for the first time.
    - Contact information for assistance with the PRS account

10.8.3 DATA ENTRY, REVIEW, SUBMISSION AND PUBLISHING OF RESULTS

The Program Analyst:

- Generates FDAAA reports from JReview
- Enters data on the PRS
- Emails a WORD copy of the data to the PI/Research Team for review
- Provides a date to return the updated WORD document (Note: The results submission deadline date and the date to return the updated WORD document are NOT the same)
- Updates data on the clnicaltrials.gov database
- Emails updated WORD document to the PI for final review and approval to submit results data

The PI approves the final version of the data to be submitted. Then, our Program Analyst will submit the record in the clincaltrials.gov database (i.e., PRS). The RP will need to log into PRS with their clincaltrials.gov username, password, and organization ID (i.e., NIHCC) to approve and release the record. At this point,

- The RP/Research Team must not edit data or allow any person to edit data on the PRS before the record is approved and released. Email the PA to make last minute changes.
- The RP must approve and release the record to complete the submission.

Once the record is submitted, approved, and release, there is a QC process that is conducted on the data. The PI and our Program Analyst may receive comments about data discrepancies and/or recommendations for changes. Our Program Analyst will the provide the PI with a WORD document to answer the discrepancies/changes to be made and a deadline. Once this is completed, data is then updated in the PRS.

Following a successful QC review, clinicaltrials.gov will notify the PI that the record update will appear on clinicaltrials.gov within 2 business days following receipt of the email.

10.8.4 COMPLIANCE

PIs must be compliant per the NIH Manual Chapter 3007 – Clinical Trial Registration and Results Reporting Information. The CC PSS tracks compliance as does our Protocol Analyst who:

- Provides the results submission deadline
- Sends email notifications to the PI and/or Research Team/Team Lead to report results
- Sends follow-up emails to PI/Research Team if data not returned
- Sends results reporting notice of non-compliance

Both the PI and the Program Analyst receive emails from PSS.

Per the NIH Manual Chapter 3007 – Clinical Trial Registration and Results Reporting Information, the Chief Scientific Officer, CC Director for Clinical Research will notify leadership in the Institute/Centers (IC's) of non-compliant protocols. Notification may include consequences for non-compliance which impact protocol development (e.g., no NIH sign off on Scientific Reviews of any new protocols). The PI then has 30 days to become compliant or leadership will start implementing other consequences for non-compliance after 30 days.

10.9 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Read CCR SOP PM-5, *Research Protocol Training Requirements*
2. Read CCR SOP PM-7, *Clinical Research Study Initiation*
3. Read CCR SOP PM-9, *Research Team Training Requirements for IRB Modifications*
4. Review M2P2 #17 *What information needs to be reported to the IRB at the time of continuing review (CR)?*
5. Review CCR SOP PM-15, *Preparation of Safety Monitoring Committee (SMC) Report*
6. Review CCR SOP RPS-20, *Preparation of Study Closure*
7. Review M2P2 #41 *What is the primary completion date (PCD) and the anticipated completion date (ACD)? Why are these dates important?*
8. Watch the FDA 3 part webinar series on ClinicalTrials.gov

10.10 ADDITIONAL RESOURCES

- Office of Human Subjects Research Protections: IRB Operations
- SOP RSP-13, *Preparation of a Continuing Review or Progress Report*
- HHS.gov Continuing Review Guidance (2010)
- IND Application Reporting: Annual Reports
- OHSRP webinars:
    - January 19, 2021: *Secondary Research: Fact, Fiction, Fears and Fantasies*
    - October 7, 2021: *Using and Sharing Existing Specimens and Data for Secondary Research: Expectations for consent and IRB Approval*

11 PATIENT RECRUITMENT AND REFERRALS

11.1 SOURCES OF REFERRALS

New patient referrals come from a variety of sources, including outside healthcare providers, self-referrals, support groups, private management companies (hired by patients or their families), the CC Office of Patient Recruitment, and patients who have previously been on a trial at the NIH.

Each research team has a system for reviewing & screening referred patients. There are two referral offices that serve the CCR, the Medical Oncology Referral Office and the Surgery Branch Immunotherapy Referral Office. These offices are the primary contact for many of the CCR branches.

11.2 GENERAL PRINCIPLES REGARDING REFERRALS

Regardless of whether teams utilize one of the referral offices, there are general principles regarding referrals. Any research team member could be the first person contacted by an outside provider, the patient, the family, or the NCI Cancer Information Service. Remember to treat the individual with patience and respect, knowing each staff member is representing NCI and NIH. Many patients or family members have anxiety placing these calls or emails and do not know how the system works. Please reply within 24 hours to all phone calls and emails regarding a referral.

Each member of the research team needs to understand how their team manages referrals. If there is a specific person on the team, connect the referring individual with the team member or forward the email as appropriate. For example, return the call or email and explain you are connecting them with the referral coordinator for your team. This way they know their call or email was received and is receiving attention.

Research teams may accept international referrals. Understand the research team's decision to accept or not accept international referrals. If the team does accept international patients, are there certain caveats per protocol? When receiving a phone call from a referral who does not speak English, return the call utilizing the CyraCom language line, see Appendix A for instructions. See Appendix B for how to make international phone calls using WebEx.

Pre-screening referrals begins with this phone call or email. Basic information is needed including the diagnosis, therapies received (if any), performance status (PS), location of patient (e.g., in U.S.? what state?) and the patient's preferred language for healthcare. It may be obvious from this first phone call that the patient is not a candidate for a trial. Below is an example:

Let's say a team's studies are designed for patients who have had at least one regimen of standard care. The caller explains they were diagnosed with cancer last week and wants to get into a certain trial. You would know that this patient is not eligible because they have not had the standard of care. How do you proceed with this referral? You will want to gently explain basic information about their type of cancer, what the standard of care is and why they are not eligible currently. Keep the options open to communicate again as they go through treatment. Keep in mind, there may be trials for newly diagnosed patients with this cancer at other institutes. There is a misperception that calling NIH in Bethesda is equivalent to checking on trials all over the country. The NCI's Cancer Information Service (CIS) also can assist patients in finding clinical trials as well as providing answers to cancer-related questions. They also provide these services in Spanish. NCI CIS contact information:

- Phone: 1-800-4-CANCER between Monday – Friday 9AM -9PM ET
- Live chat: https://livehelp.cancer.gov/ Monday - Friday 9AM -9PM ET
- Email: NCIinfor@nih.gov.

If you think the patient is potentially eligible following this initial contact, the next step is a review of medical records. Obtaining records may be done by the patient, the referring doctor and/or CCR staff referral office. Think about what records are needed to determine eligibility for your trials. In general, the following records are needed to prescreen for eligibility:

- Pathology reports including genomic and/or molecular testing
- Radiology reports documenting measurable or evaluable disease, as appropriate per protocol
- Recent lab results including CBC and chemistry, tumor markers, if appropriate
- Provider notes with details of patient's medical history, course of treatment, physical exam, medications, and current PS
- Contact information for the patient

Occasionally these records are also needed:

- Operating Room (OR) reports
- Radiation therapy summaries
- Chemotherapy flow sheets if the details are not present in the provider notes
- Other specialty notes e.g., cardiology if there is a cardiac history.

If the team is helping obtain records from outside institutions, here are some tips:

- To e-fax from Outlook:
    - Click on "New Email" and in the "To" field, type in the name of the institution, followed by %9-1-*insert 10 digit fax number*@fax.nih.gov.
      (i.e.: MedicalRecords%9-1-301-555-5555@fax.nih.gov)

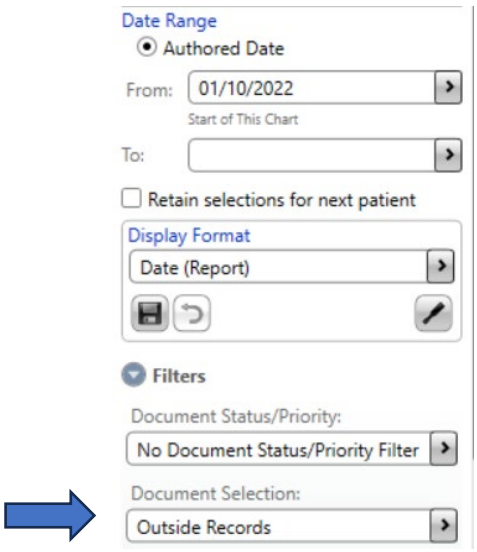
    - Include the patient's name and date of birth, a list of needed records, purpose of the records request, where records may be sent, and who from the research team to contact with any questions
    - The sender will receive e-mail confirmation whether the fax went through or not, but it is still a good idea to follow up with the outside institution to ensure the request was received
- Outside institutions may require a signed release of information from the patient. They may require their own institution's form to be completed by the patient or they may accept the NIH-1208 *Request for Medical Information from Sources Outside the National Institutes of Health.* Ask them if you are not sure.
- The CCR Referral Application database has fax templates and stored fax numbers that (see Section 11.3)

If the patient seems like they may be potentially eligible based on the record review, the radiology images are then reviewed by the PI or designee, sometimes as part of a multidisciplinary process. Images may be transmitted to NIH CC drop box, by the patient or the referring provider. More often the images are sent to the research team, usually the CRC, via FedEx. See DCRI website for instructions on using Box to upload films.

Following the records and imaging review, a decision is made to invite the patient for a screening appointment, or the patient is determined to be "not eligible". The research team notifies the referral point of contact, whether it's the patient, family member or provider, explaining the outcome of the records review.

If the patient's preferred healthcare language is not English, language access services arrangements must be made. Please see MAS Policy M23-2 Language Access in the Clinical Center for more information. Medical records and/or protocol consents may need to be translated so research teams must plan accordingly. See section 12.8 for more information.

If the referral is an established NIH patient, research teams may review their existing records in CRIS for eligibility, including previously obtained outside records that were uploaded. Open the patient's chart in CRIS, select the "Documents" tab, on the left side under "Filters," click on "Document Selection" and select "Outside Records." Be sure to choose the appropriate Date Range to see records. Please be sure to review only the amount of PII necessary to determine eligibility.



If pathology confirmation is required for eligibility, patients must be enrolled on an appropriate protocol prior to submitting material to pathology. This will require informed consent (may be done remotely) and External Location (also referred to as "ex loc") registration, if they are a new NIH patient. There are processes in place for both and protocols should allow for this. See CCR SOP ADCR-13 *Clinical Center External Location Registration and Subsequent Activities* for details.

Some research teams offer consultation visits if the patient is not currently eligible for a protocol. Be aware if your team offers consultation visits and what that process involves. Your team may use protocol 04-C-0165 for medical consultation purposes. This protocol is also used throughout the CCR to provide standard of care treatment or follow up of disease, screen donors of cellular products and genetic follow up.

Once a patient has been registered as an NIH patient as above, the CRC or other members of the research team may upload all outside records to CRIS that are pertinent to either clinical care or research. For more information, see CCR SOP PM-4 *Submitting Outside Records for Entry in CRIS.*

11.3 THE MEDICAL ONCOLOGY REFERRAL OFFICE (MORO)

The MORO is the referral point of contact for many research teams within the CCR. This office assists in the gathering of medical records, scan images and pathology materials. The MORO is a paperless office, requesting and receiving records via an e-fax. No paper records are sent to MORO. MORO will request radiology images and pathology materials be sent to the research team. No scans or pathology materials should be addressed to staff in the MORO. MORO reviews records for completeness and general eligibility. Specific eligibility concerns are communicated to the research team.

Records received will be bookmarked in Adobe and placed in the CCR Referral Application: https://ccrreferrals.nci.nih.gov/. If your team utilizes MORO, please review the *CCR Referrals Application Training Guide*. MORO will notify the research team when records are received. MORO will copy and paste email strings and document telephone conversations related to the referral in the *Notes* section of the referral application. The research team is also encouraged to document phone calls, correspondence, and record review outcomes in the referral application so all research team members and MORO can follow the progress of the referral. The research team will document in the CCR Referral Application when scans and pathology materials are received. MORO does not consent patients to any protocols or obtain Ex Loc consents. MORO does not request pathology from countries outside the United States. That is the research team's responsibility.

If your team works with MORO, it is your team's responsibility to update MORO about new protocols, status of cohort enrollments, modifications, holds on enrollment and study closures. For example, when a new protocol opens, the research team sends an email to MORO explaining the patient population, key details about the protocol and eligibility, and specifics about pathology tissue requests.

11.4 THE SURGERY BRANCH IMMUNOTHERAPY REFERRAL OFFICE

The Surgery Branch (SB) Immunotherapy Referral team is the referral point of contact for the Surgery Branch Immunotherapy group within the CCR. They speak with patients and referring providers, educating them about surgery branch trials, gathering records, CDs of scans, and pathology material. They will also place records in the CCR Referral Application so that the MORO and other teams can have access to the records, as many patients will want to see if there are other potential NIH trials.

Prospective patients first contact is usually with the PCC via phone call or via email irc@nih.gov or 1-866-820-4505. Patients and other physicians also contact Dr. Rosenberg or one of the other attending physicians and they forward referrals to the Surgery Branch referral office. The Surgery Branch website has an eligibility screening application that can be filled out online and sent directly to the mailbox: Surgery Branch Immunotherapy Clinic Application Surgery Branch FAQ | Center for Cancer Research. Email communication is encouraged as the first contact, as this is the pre-screening.

SB referral office is different than the MORO as they do receive and review all the records, CDs of scans, pathology slides/blocks, and blood for HLA typing in the office. They gather, review, and create a chart with a summary to the PIs for their review. Most patients have had numerous treatments and surgeries often at various facilities, so obtaining records and pathology material can be difficult. Surgery Branch referral nurses are also responsible for ex loc registrations/consenting for potential patients to obtain the pathology and blood samples for screening. Their protocols involve a form of T-Cell adoptive transfer. This requires critical review of the images and the molecular pathology (genetic reports) identifying specific mutations present on tumors. This is in addition to review of the progress notes, laboratory reports, operative reports, and treatment notes. SB referral nurses will usually ask for at least the last 3 notes and scans (images and reports) as they assess the pace and course of the disease.

SB referral nurses meet and consent patients on their screening protocol when they come to NIH for screening visits. They arrange all screening visits, orders, and schedule the necessary labs and scans after review with the PIs. They work closely with the CRCs and fellows on the team to inform them of the schedule (both by email and One Note) as they meet with the patients in clinic and will be responsible for the patient moving forward.

SB referral nurses are responsible for reviewing any modifications on the active protocols that may change the process, such as a change in the patient population, details about the study and eligibility, and specifics about pathology tissue requests, etc. They have developed general standard responses, but also individualize the responses for each patient situation. If a patient is not eligible after review from the senior staff, they are responsible for letting the referral or MD know and explain the reasoning. They often work with a patient over a long period of time, as they may continue to check in after progressive disease for another screening.

11.5 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Determine how referrals are processed in your team (i.e., utilizes one of the referral offices or receives referrals directly)
    a. Determine if there is a specific individual(s) assigned to this task
2. Determine your role within your team, as it pertains to referrals
3. Read 04-C-0165 Protocol and Consent
4. Find existing records in CRIS
5. Review the process of using the Cyracom language line. See Appendix A.

12 INFORMED CONSENT

The cornerstone of clinical research today is that of the informed consent process. History has taught both investigators and research participants many valuable lessons. Informed consent is more than just a document. Informed consent is having the capacity to agree for oneself to participate in a specific situation, a clinical research study, once risks and benefits are understood. It is an ongoing process of communication and mutual understanding between an individual and the investigator. The participant's initial agreement to participate in the clinical research study is evidenced by signing an IC document.

Consent may only be given by individuals who have reached the legal age of consent (≥ 18 years old, unless a minor has been emancipated and we have the legal document to support it.) For children, consent is obtained from the parent or guardian. For adults who are unable to make their own decisions regarding research participation, a legally authorized representative (LAR) is needed. Research teams may not enroll or involve a subject in any research activities, until legally effective informed consent has been obtained.

Prior to the potential participant signing a consent, there are minimal risk screening activities that may be done:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos

- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

However, for any other screening activities, consent must be obtained first. Note that some observational studies may only have screening activities that occur prior to consent. Refer to your protocol for what is allowed prior to and then after consenting.

Any individual who obtains consent to a protocol, should be included in the screening log. See section 12.12 for more details on screening and enrollment logs.

Both the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) regulations address informed consent:

- DHHS: Title 45 Part 46 *Protection of Human Subjects*, specifically §46.116 & §46.117
- FDA: 21 CFR Part 50 *Protection of Human Subjects*

As a reminder, the research protocol must specify the use of the following special consent circumstances, if applicable:

- Use of short form consent for non-English speaking participants
- Use of remote consent process
- Enrollment of minor participants, including assent from the minor participants
- Enrollment of adults unable to consent, including assent of participants
- Enrollment of NIH employees

To learn more about informed consent, please refer to:

- *Informed Consent* online learning module
- HRPP Policy 301 *Informed Consent*
- HRPP Informed Consent FAQs
- HRPP 400 series which describes what populations are considered vulnerable per the regulations (e.g., pregnant women/fetuses/neonates, prisoners, and children), NIH staff and those with diminished or no capacity to consent
- Five SOPs regarding Informed Consent under CCR SOP PM-2
- OHSRP webinar *Informed Consent Procedures in the Era of Covid-19: Beyond the Use of a Standard Written Consent Document*
    - Link to videocast
    - Link to slides
- OHSRP webinar *Informed Consent One Year after the 2018 Common Rule Revisions: Updated Information and Processes*
    - Link to videocast
    - Link to slides
- Monday Morning Practice Pearls (M2P2): Search by topic - informed consent and FAQs

12.1 INFORMED CONSENT DOCUMENT (ICD)

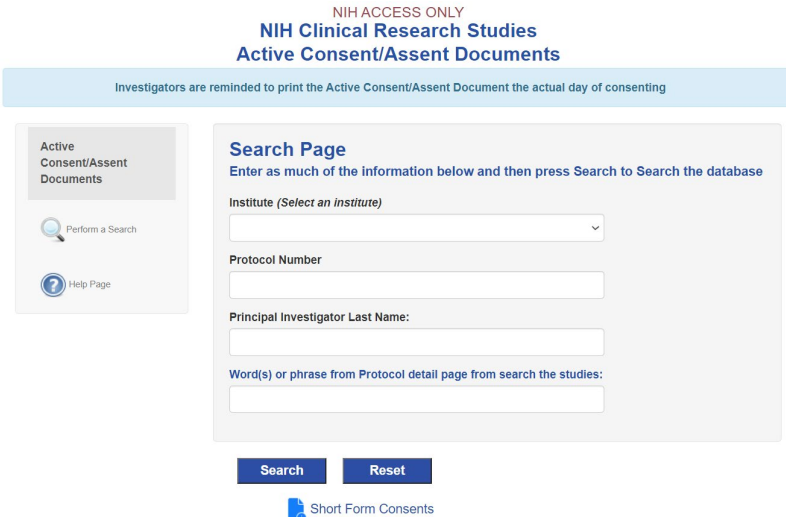
The informed consent document (ICD) is the IRB-approved written record that is compliant with the regulations and is used to demonstrate the consent by a subject/LAR to participate in research. It explains what will be done and the subjects' rights. It should be written in a language understandable to the subject and contain no exculpatory language. The PI and the PSO manager will develop the ICD, but all investigators should read and be familiar with the contents of the ICD since that is what the patients will be given and where they will draw some of their questions from.

The NIH IRB has several ICD templates found on their *Consent Templates and Guidance* website. This site includes templates for:

- NIH CC
- Off-site (i.e., when enrolling a subject who will never come to the CC)
- NCI CIRB
- Model consent (i.e., when NIH is the lead site in a multi-site study)
- Expanded access

IRB-approved ICDs can be found at 2 sites:

- CC's NIH *Clinical Research Studies Active Consent/Assent Documents* website



- CRIS, if iMedConsent™ is in the approved IRB protocol. The research protocol or NIH Addendum must specifically allow for the use of iMed. See *User Guide iMedConsent™*.

12.2 STAFF WHO MAY CONSENT

Not all clinical research staff will be able to consent. The PI is ultimately responsible to ensure that informed consent is obtained consistent with regulations and the reviewing IRB and NIH IRP human research protection program's (HRPP) policies. However, the PI may delegate obtaining consent from prospective subjects to other qualified persons. The delegated study staff member needs to be:

- Familiar with the protocol, research, and clinical experience;
- Able to assess the potential subject's capacity to consent;
- Have appropriate training in human subjects research protections (i.e., the CITI Biomedical 101 and GCP courses). This is outlined in *HRPP Policy 103 Education Program*;
- Listed in the IRB protocol application process (PROTECT) with assigned task of informed consent; and
- Listed on the delegation of tasks log

Ideally, the staff member being delegated to consent should have observed the informed consent process by the PI or another investigator a few times and then have the PI observe them obtain consent before being delegated that task.

Trainees who are not federal employees (e.g., IRTAs, CRTAs, VFs) and Special Volunteers (V) may observe and participate in the IC process under direct and constant supervision by a qualified NIH employee investigator. These trainees may not sign the informed consent document. The NIH employee investigator supervising the IC process must sign the informed consent document.

12.2.1 CAPACITY ASSESSMENT

Capacity is having the ability to make a decision for oneself at a point in time. For research consent, this is a one-time clinical judgement of an individual's ability to give informed consent. Capacity to give informed consent may fluctuate over time. In comparison, competence is the ability to understand legal rights and responsibilities and the possession of authority to make legal decisions. The determination that someone is not competent is made by the court.

Common domains of capacity assessment include:

1. Understanding: Understanding of disclosed information about the nature of the research project and its procedures
2. Appreciation: Appreciation of the effects of research participation (or not participating) on subject's own situation
3. Reasoning: Using the information in reasoning
4. Choice: The ability to communicate a choice

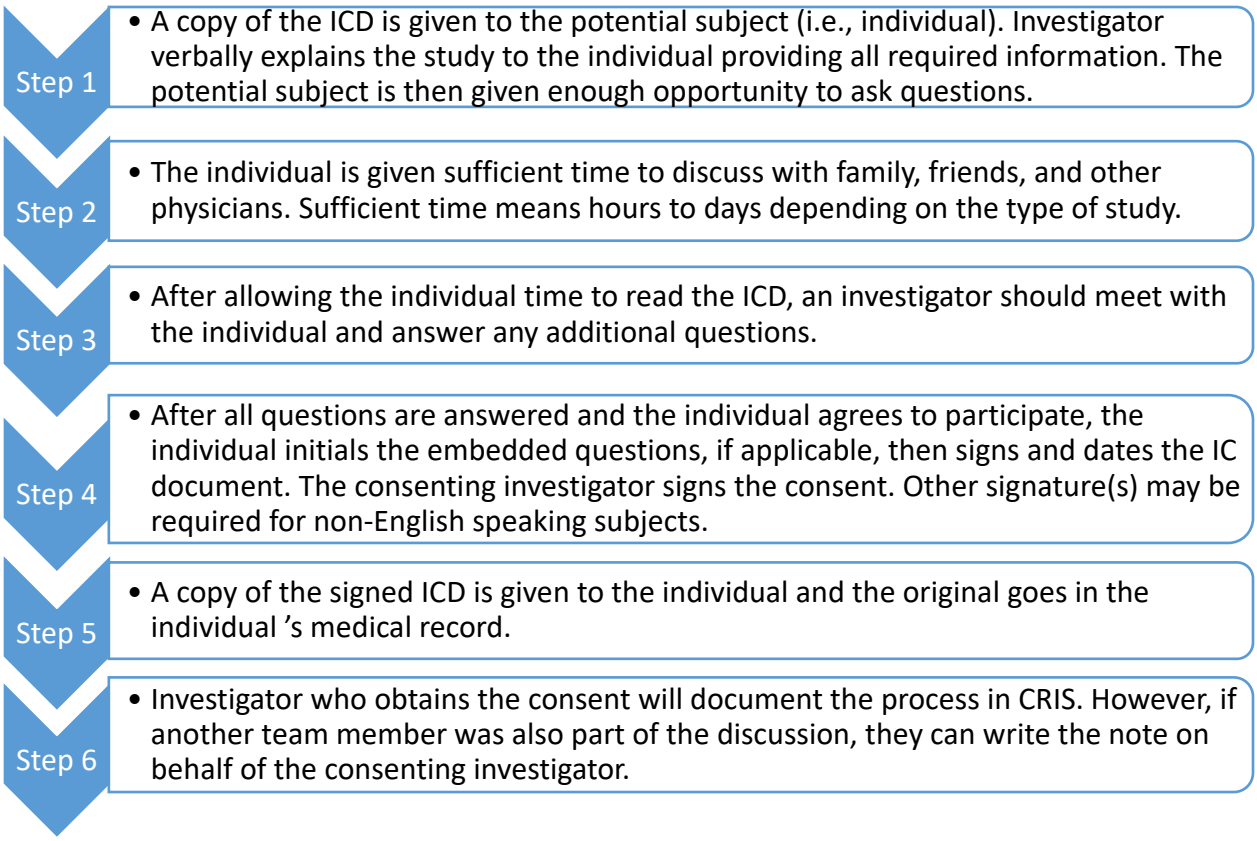
The HRPP Policy 403 *Research Involving Adults Who Lack Decision-making Capacity to Consent to Research Participation provides* describe the additional safeguards and considerations that apply to those subjects without capacity to consent.

If any staff is unsure of an individual's capacity to personally consent to research, they should consult the Ability to Consent Assessment Team (ACAT) to make a capacity assessment. ACAT is a joint function of the Bioethics Consultation Service and the Human Subjects Protection Unit of the National Institute of Mental Health. The team can determine if the prospective subject has the capacity to consent to research participation, the capacity to assign a Durable Power of Attorney (DPA), and, when needed, to assess and determine if a Legally Authorized Representative (LAR) is appropriate. To request a Bioethics consult including capacity assessment, use any of the following approaches:

- Call the Department of Bioethics main number at 301-496-2429
- Call the NIH paging operator at 301-496-1211
- Put a request in the Clinical Research Information System (CRIS)
- Ask for the name of the consultants on call at 301-496-2429, and send them an email

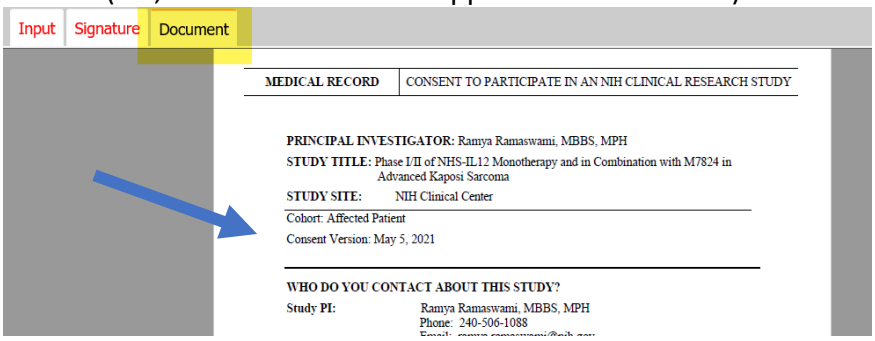
12.3 INFORMED CONSENT PROCESS

Below is a schematic of the informed consent process.



If using the iMedConsent™ to secure the signatures, the consent process is essentially the same as above, including step 1, except for the signatures. Before using the electronic signature process for iMedConsent™, follow the steps below:

1. Read the *User Guide iMedConsent™*
2. View the training video
3. View the *Patient Mobile Signature Education Video* so that you can help your patient if they have questions
4. Have the patient view *Patient Mobile Signature Education Video*
5. Begin the discussion. Note, the potential participant should have already received a copy of the consent document as per Step 1 above.
6. Open the protocol specific iMed consent and make sure that you are using the correct version (i.e., the most recent IRB approved IC document) from the Document tab



7. Review the document in its entirety with the patient and confirm that all information entered on the Input tab is consistent with the participant's preferences
8. Secure initials for the embedded questions, if applicable, and the signatures. See *User Guide* page 11, section entitled "Obtaining signatures"

12.4 IN-PERSON CONSENTING

When obtaining consent in person, the discussion should occur in a private setting, the signatures obtained after the discussion and a copy of the signed consent given to the patient. The signed ICD is then sent to HIMD for uploading into CRIS and quality control. If iMed consent process is used the consent will automatically be uploaded to CRIS (i.e., no need to send to HIMD).

12.5 REMOTE CONSENTING

Remote consenting can be either via telephone or synchronous audio/video process. The protocol needs to describe and justify the process. Only NIH-approved platforms, currently ThinkAndor®, can be used when conducting a consent via video or telehealth. Informed consent is not valid until the signed document is returned.

No research procedures may be initiated until the participant has returned a signed and dated informed consent document except if the IRB:

- Has granted a waiver of documentation of consent OR
- Has approved the information and/or sample (e.g., a survey, blood collection or buccal swab sample) to be collected remotely and returned along with the informed consent document. No use or analysis of the information or sample may begin until a fully executed IC document has been received and verified by an investigator

Below is the process used for remote consenting which is also outlined in CCR SOP PM-2:

- Send current IRB approved ICD to patient and set up time to discuss
- Confirm ID of patient
- Review entire ICD
- Ask patient if they agree to participate and ask them to sign and date the consent while you are still either on the phone or in a telehealth visit with them. If you don't have them sign and initial embedded questions at this time, you will need to reconsent the patient or by default, the blank answers are considered "no."
- If the patient "needs to think about it," you must set up another time to hear the patient verbally agree to participate – this is NOT verbal consent
- If the patient returns the consent via fax or secure email, that consent becomes the "original" that the investigator signs
- The **entire** consent should be returned, not just the signature page(s)
- The investigator obtaining consent signs the returned consent and dates ***the day the consent is received*** (NOT the date of the telephone conversation unless the signed consent is received the same day). If the short form process was used, the witness will also sign once the consent document is returned with the date the consent was received. Note: when using iMed, all signatures are obtained in the iMed system at the time of the IC process. The signature of the investigator obtaining consent must be done after the participant, parent and/or LAR signature/initials are captured in the iMed system.
- Within 1 day of the telephone conversation, complete a *Documentation of Research Consent* progress note in CRIS
- The date of the telephone conversation during which a patient agrees to participate in the study is the date of consent. *Note: this is the date that you will enter into the Protocol Registration and Enrollment System (PRES).*
- If the signed consent has not yet been returned, only include the relevant information in the note, then update the note once the consent is received.

Visit the following OHSRP websites for more information on remote consenting and telehealth visits:

- *Obtaining Consent Using a Remote or Other Alternative Process* for additional guidelines and sample language
- Policy 303 *Intramural Research Program Telehealth Requirements*
- CC MAS Policy M20-1 *Utilization of Telehealth/Telemedicine by NIH Healthcare Providers for NIH Clinical Center Patients*

12.6 ASSENT

Assent is a term used to express willingness to participate in research by a child (<18 years of age) or an adult with diminished capacity who are old enough or able to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects to give legal consent to participate in the research activity.

Assent by itself is not sufficient. If assent is given, informed consent must still be obtained from the subject's LAR. Failure to object to participation should not be construed as assent and would need further discussion with the potential subject.

For children, the regulations (i.e., 45 CFR 46.408 & 21 CFR 50.55) allow the IRB to waive the requirements if:

- some or all of the children will not be capable to provide assent; or
- under some circumstances, when the study holds out the prospect for direct benefit that is important to the health or well-being of children, and is available only in the context of research; or
- the research meets the same requirements as waiver of consent.

Based on these regulations, the IRB may feel that permission, or consent, of one parent is sufficient but both parents may need to be consented if the research is approved under other regulations (i.e., 45 CFR 46.406 & 21 CFR 50.53 or 45 CFR 46.407 & CFR 50.54). However, at the CC, when parents share joint legal custody for medication decision-making both parents must give consent.

The IRB expects that the investigator will submit a proposal in the protocol, describing which age groups will be able to provide assent, and which will not. This should be based on the type and complexity of the research, and the population being enrolled. Children too young to assent should still have the research explained to them in terms appropriate to their level of understanding and maturity.

The NIH IRB has additional information and an assent template on their *Assent Template and Assent Information* website. Please see the CCR FAQs regarding translation of assent.

12.7 WAIVER OF CONSENT

The IRB can approve consent processes which does not include, or which alters, some or all of the elements of informed consent. They can even waive the requirement to obtain IC from some or all of the research subjects if all of the following criteria are met:

- Research involves no more than minimal risk to the subjects;
- Waiver or alteration will not adversely affect the rights and welfare of the subjects;
- Research could not reasonably be carried out without the waiver or alteration; and
- Whenever appropriate, subjects will be provided with additional pertinent information after participation.

There are also some types of protocols where a consent is not needed since the patient already consented to future use of their data or specimens. These include retrospective chart reviews and secondary use protocols.

12.8 NON-ENGLISH-SPEAKING SUBJECTS/LIMITED ENGLISH PROFICIENCY

There are 2 situations that might arise when a non-English speaking subject or a subject with limited English proficiency will be enrolled in a clinical research study:

- PIs anticipate this to happen based on the study population. This should be the more common scenario as research teams often have multiple conversations with prospective research participants, their caregivers and/or referring providers prior to study enrollment. Research teams need to assess preferred healthcare language early so they can make appropriate translation and interpreter accommodations for the participant's research participation at NIH. Just because a participant speaks some English does not mean this is the language they prefer to have healthcare encounters in, so it is important to ask.
- PIs don't anticipate this to happen. This means that the research team could not have reasonably known that they might enroll a person who doesn't speak English, has limited English proficiency and/or has a different preferred healthcare language.

Regardless of whether anticipated or not, if the investigator consenting the subject is fluent in that subject's language, then the consenting discussion is the same as if being conducted in English. However, if the consenting investigator is not fluent, then a professional medical interpreter will be needed.

The following M2P2s provide overviews of these 2 processes:

- M2P2 #24: *You learn that your patient doesn't speak English and you don't have an IRB-approved protocol consent in the patient's native language. What do you do? Part 1: Seeking IRB Approval & Securing Interpreter*
- M2P2 #25: *You learn that your patient doesn't speak English and you don't have an IRB-approved protocol consent in the patient's native language. What do you do? Part 2: Consent Discussion and Documentation*
- M2P2 #26: *You learn that your patient doesn't speak English BUT you have an IRB-approved protocol consent in the patient's native language (i.e., the full English version translated). How does the consenting process differ when not using the short form consenting process?*

12.8.1 INTERPRETER SERVICES

Whenever possible, a professional interpreter, who is in-person, should be used or, alternatively, professional interpreter can be via a phone interpreter service. Use of a family member for interpretation is not permitted unless a professional medical interpreter cannot be located. The reasons for using a family member and the attempts made to locate a professional interpreter must be documented in the research record. Family members may not have adequate medical knowledge and are not trained as professional medical interpreters. Additionally, family members may not be impartial or may try to speak for the subject which can limit the subject's decision-making process. In this situation, the investigator must document in CRIS the reasons for using a family member and the attempts made to locate a professional interpreter.

The CC Social Work Department has a Language Interpreters Program. To schedule an in-person interpreter, please place an order in CRIS for *Language Interpreter - Social Work Department* no later than 24 hours prior to the date the service is required. Please note that some languages may require more than 24 hours to secure an interpreter.

The Cyracom Telephonic Interpreters services is used when in-person translator is unavailable. See Appendix A for information on Cyracom.

12.8.2 TRANSLATION SERVICES

The NIH Library Translation Services and its contractors provide written translations of materials including ICDs and certificates of accuracy. There are fees associated with the translation of documents. The PSO manager will make the request for all translations of an informed consent document or an assent document.

12.8.3 ANTICIPATED ENROLLMENT

When non-English speaking subjects are anticipated to enroll in a particular research protocol, for both minimal risk and greater than minimal risk research, there must be a certified translated long form consent document in the language of the anticipated subjects and an IRB approval of the certified translation must be obtained before the translated long form can be used. The prospective participant's enrollment in a study may need to be delayed to obtain the translated document, unless it is clearly in the prospective participant's best interest to not delay and proceed with enrollment using the short form process.

12.8.4 UNANTICIPATED ENROLLMENT – SHORT FORM PROCESS

When a non-English speaking subject seeks to enroll in a study, it is unanticipated and there is no IRB-approved long form consent document in the language of the subject, the investigator must use an IRB-approved short form consent document in the language of the subject, if one is available.

If the specific study to which the individual will be consented is known:

- PSO will submit the request for translation of the long study consent for the specific study for greater than minimal risk studies.
- PSO will consult with OCD leadership and determine if to submit a request for a short form translation or if to submit a request for translation of the consent for minimal risk studies.

If the study to which the individual will be consented is not yet known and/or the long form consent will take too long to be translated, PSO will request that a short form be translated ASAP. The individual cannot be consented/enrolled until the short form is translated.

For research determined by the IRB to be minimal risk:

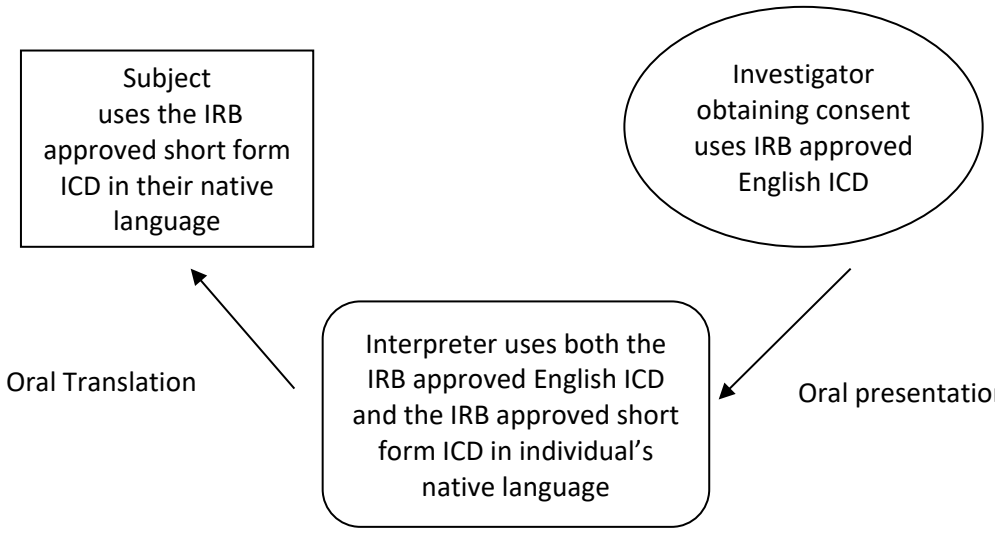
- If a non-English speaking person is encountered that is eligible for enrollment and there is no translated consent document, the short form process may be used.
- The research team must inform the IRB of the use of the short form within 7 calendar days by submission of a Reportable New Information (RNI) form in PROTECT. This should be done for each use of the short form. For those studies which require continuing review, cumulative short form use must be provided at that time.
    - Select "Short Form Use" on the RNI form.
    - Provide the justification for using the short form consent process in the description of the event.
    - Inform the IRB if the translated consent will be provided to the participant.
- If the short form process is used 3 times for a given language, the short form process may no longer be used for that language, and the consent must be translated for any future participants that speak that language.

For research determined by the IRB to be greater than minimal risk:

- If a non-English speaking person is encountered that is eligible for enrollment and there is no translated consent document available, enrollment of that individual should be delayed and an IRB approved translated consent obtained, UNLESS it is determined by the Principal Investigator that it is justified to proceed because it is in the prospective participant's best interest to enroll prior to the translation.
    - The best interest of the subject means that it is necessary to ensure the rights, welfare, and safety of the prospective participant. For example: i. A trial with therapeutic intent and there is insufficient time to obtain the translation due to the rapidity of disease progression or severity of the underlying disease.
    - Delaying consent would pose undue hardship on the prospective participant, for example due to travel distance, need for time off work or away from responsibilities at home, etc.
    - The convenience of the research team or cost of translation are not sufficient justification.
- If the PI determines it to be justified to proceed with informed consent prior to translating the consent, this determination and the reasons for it must be documented in the research record and/or CRIS as part of the consent note.
- If the determination is made to proceed prior to translation of the consent, informed consent should be obtained and documented using the short form process.
- In addition to reporting short form consent use at time of Continuing Review (CR), the IRB must be informed of the use of the short form within 7 calendar days by submitting a Reportable New Information (RNI) form in PROTECT.
- If the non-English speaking person has agreed to participate using the short form process, the consent MUST be promptly translated into the participant's language, submitted to the IRB along with the certificate of translation and, after IRB approval, be provided to the participant. This is not considered a reconsent, so therefore the participant does not have to re-sign. However, it is expected that any questions that may arise after the participant reviews the translated consent will be answered.

For more detailed information, please refer to the CCR FAQs.

Below is a schematic of what the short form process entails:



When the short form consent process is used, there must be a witness who is present for the entire oral consent presentation. The witness must be fluent in the language of the subject and in English. The witness must be present at the location of the Investigator obtaining consent. Either the interpreter or a second individual (fluent in both languages) can serve as the witness.

12.9 SPECIAL INFORMED CONSENT SITUATIONS (BLIND, DEAF, ILLITERATE OR UNABLE TO SIGN)

When the patient speaks and understands English but is illiterate or blind, the English long form should be used to obtain consent from the subject. The short form consent document should NOT be used. The subject may use assistive technology (such as screen readers for sight-impaired individuals) to read the consent, or the consent form should be read to the subject. There must be a witness to the entire oral presentation of the consent. The witness then signs the witness line on the English long form consent. Subjects who are unable to sign their name can make their mark (i.e., an "X" or provide a fingerprint). The consent note in CRIS should document the process and include a statement that there was a witness to the entire consent process and any special circumstances regarding documentation of consent. Sign language interpretation are available for the hearing impaired by contacting The Office of Research Services.

12.10 INFORMED CONSENT DOCUMENT SIGNATURES

There may be several signatures needed on an ICD. Below is a table outlining what signatures are required and in what situations.

Signature	Use of Long Form[1]	Use of Short Form	Assent
Subject/LAR	Signature required	Signature required on the short form	Signature required of subject only
Investigator obtaining consent	Signature required	Signature required on the English long form	Signature required
Witness	N/A	Signature required on both long and short forms	N/A
NIH administrative section	Needs to be completed for non-English long form	Needs to be completed on both the long form and short form and they must match	N/A

[1] Long form refers to the IRB approved English ICD or the fully translated IRB approved non-English ICD

For embedded questions:

- The subject/LAR will initial the questions when the long form only is used
- For the short form process:
    - Investigator obtaining consent answers on behalf of the patient
    - Interpreter asks the patient the embedded question(s) and tells the investigator their response
    - Investigator indicates the response on the long form by initialing the patient's response using the investigator's initials
    - If patient declines to answer, the embedded question(s) are left blank
    - Neither the interpreter nor the subject/LAR should record a response for the embedded questions
    - *Documentation of Research Consent* note must clearly explain the review and response of embedded questions

12.11 DOCUMENTATION OF THE INFORMED CONSENT PROCESS

Once the consenting process is complete and all signatures secured, a note needs to be written in CRIS ideally by the consenting investigator or by another person who was present during the process and who can document in CRIS. This is consistent with both the HRPP Policy 301 and CCR SOP PM-2. The CCR SOPs also state that:

- Documentation of the informed consent process must be completed in the medical record **within 1 business day** of the informed consent document being signed, if in person.
- If the informed consent process takes place remotely, documentation of this process must be initiated **within 1 business day** of participant agreeing verbally to participate and updated when the signed IC document is returned.

The CRIS structured progress note *Documentation of Research Consent* must be used. The consent note has 5 tabs: protocol ID, consent type, other populations, consent process and comments. After selecting the protocol ID, select ALL the consent types used during the informed consent process:

- Use of iMed platform
- Use of interpreters (including staff and other parties)
- Use of assent
- Short Form consent
- Use of LAR and/or parents
- Telephone consent (paper consent only)

Based on the type of consent, additional information will be collected in the note. If none of these apply, just click on tab or ">" to advance to *Consent Process* tab.

In the *Consent Process* tab, there are pre-populated statements that you can select to document the process – select "Yes" or "No." If "No" is selected, a text box will appear that requires an explanation. For example, in a remote consent not using iMed, the staff member cannot select "Yes" to the statement "A Copy Of The Consent, Signed And Dated By The Investigator And Participant Was Given To The Participant." Select "No" and the reason would be "remote consent process used," Once the signed ICD was received, the Investigator signed and dated the ICD and a copy of the ICD was given to the subject, then document this statement as a "Yes."

At a minimum, the following should be included:

- Protocol number and/or short title
- Date consent was obtained.
- The study was discussed, and questions were answered.
- A copy of the consent/assent document was provided to the study participant or LAR.
- The consent was obtained prior to any research procedures being performed.
- If applicable, oral consent or consent of non-English speaking participant was performed. In these cases, include name of interpreter, if used.
- Assent process used for minor participant, as required.

12.12 SCREENING AND ENROLLMENT LOGS

Screening and enrollment logs are essential documents that track all research participants who have signed a consent to screen and/or have enrolled in the study. They will contain information about screening duration and date(s) of consent(s), subject study number, cohort/arm enrollment if applicable, and/or the reason why a potential participant was not eligible for a study (otherwise known as "screen failure"). There may be 2 separate logs, one for screening and the other for enrollment, or they may be combined. Depending on the sponsor, they may or may not contain PII. CRCs typically start and maintain these logs.

Study sponsors may have their own screening and enrollment log template that is required for use by the site. That log template should be provided before or at the time of site initiation visit.

For CCR-held INDs, OSRO requires the use of their Participant Screening and Enrollment Log. The log and instructions can be found on their website.

For non-IND intervention studies and observational studies that do not have a Sponsor, the research team may use the Screening and Enrollment Log template found on the CCR wiki.

12.13 RECONSENTING

If informed consent is an ongoing process, what does it mean to reconsent? Reconsenting means that after discussion, the subject/LAR makes the decision to participate once again in the research. Typically, this means re-signing the latest IRB approved ICD.

While there are no regulatory requirements that address the issue or process for "re-consenting" subjects during a study, there are regulations (§46.116[c][5] and §50.25[b][5]) related to promptly providing new information that becomes available during the conduct of a study which might affect the subject's decision to continue in the research.

The following are some situations which may require reconsenting:

- Identification of new research-related risks
- Increase in the frequency or magnitude of previously described risks
- Unanticipated problem that exposes subjects to new risks
- Decrease in expected benefits to participation
- Change to the research that results in increased burden or discomfort
- Availability of new alternative therapies
- Change in investigational drug dosage or device application or in exposure to the drug/device
- Change in duration of the subject in the trial or other changes likely to increase the burdens or discomforts of participation
- Change in use of specimens obtained in the research
- A subject did not sign the ICD or an inappropriate LAR signed the ICD
- Changes to medical treatment choices if research subject is injured due to the study
- Change in the financial burden of participation
- Changes in the investigator's financial conflict of interest

The IRB or IND/IDE sponsor will let PIs know if reconsenting is required. This may come in the form of just informing subjects about something new and documenting in CRIS and/or once the amended ICD is approved, having them re-sign the ICD. If re-signing is required, don't forget to also update the date the consent was signed in PRES. For a one-page overview of this process, see M2P2 #27 *If consenting is an ongoing process, what does re-consenting mean?*

If the IRB has determined that reconsent is required, non-English speaking participants must be provided this information in their own language. In some cases, this may be accomplished by creating a translated consent addendum that addresses the changes, and providing this addendum to the non-English speaking participant, rather than translating the entire document. If the changes are extensive, the full modified consent document may need to be translated.

12.14 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete the *Informed Consent* online learning module
2. Read HRPP Policy 301 *Informed Consent*
3. Read HRPP Informed Consent FAQs
4. Read the five (5) SOPs under CCR SOP PM-2 through PM-2d
5. View the OHSRP webinar *Informed Consent Procedures in the Era of Covid-19: Beyond the Use of a Standard Written Consent Document*
6. View the OHSRP webinar *Informed Consent One Year after the 2018 Common Rule Revisions: Updated Information and Processes*
7. Read the *User Guide iMedConsent™*
8. View the iMedConsent™ training video
9. View the *Patient Mobile Signature Education Video*
10. Read M2P2 #24: *You learn that your patient doesn't speak English and you don't have an IRB-approved protocol consent in the patient's native language. What do you do? Part 1: Seeking IRB Approval & Securing Translator*
11. Read M2P2 #25: *You learn that your patient doesn't speak English and you don't have an IRB-approved protocol consent in the patient's native language. What do you do? Part 2: Consent Discussion and Documentation*
12. Read M2P2 #26: *You learn that your patient doesn't speak English BUT you have an IRB-approved protocol consent in the patient's native language (i.e., the full English version translated). How does the consenting process differ when not using the short form consenting process?*
13. Read M2P2 #27 *If consenting is an ongoing process, what does re-consenting mean?*

12.15 ADDITIONAL RESOURCES

- OHRP Informed Consent FAQs
- OHRP Informed Consent videos
- Guidance for obtaining consent to participate in research from non-English speaking participants (OHSRP under Policy 301)
- CCR FAQs

13 SOURCE DOCUMENTATION

Source documents are original documents, data, or records created during a clinical study which relate to the medical treatment and history of the participant. Any document in which study information, observations, or data is recorded for the first time is source material. Examples of source documents:

- outside medical records

- all internal medical documentation
- research reports, records, and documents throughout a study
  - consent forms
  - participant diaries
  - adverse event and medication logs

To learn more about essential documents, please refer to part 1 of the *Documentation and Document Management* online learning module.

13.1 CLINICAL RESEARCH INFORMATION SYSTEM (CRIS)

The Clinical Research Information System (CRIS) serves as the NIH Clinical Center's electronic health record (EHR) which is based on the commercial product from Allscripts called Sunrise Clinical Manager (SCM). Other NIH CC clinical information systems are integrated into CRIS:

- Laboratory Information System (LIS)
- Radiology Information System (RIS)
- Radiology Viewing System (PACs)
- Electrocardiogram (EKG)
- Health Information Management System (e.g. transcription, scanning, incomplete record tracking, release of medical information, diagnostic and procedure coding)
- Surgical Information System (POIS)

CRIS resources include:

- Learning Resources website provides excellent reference materials, FAQs, CRIS "How-To" videos, and other helpful information.
- CC Chief Information Officer (CIO) newsletter which is sent out monthly and provides updates about CRIS and other tips for using CRIS. Visit the CIO Newsletter website to see current and previous versions.

CCR ORN's website also has resources under the Computer Corner page. This includes:

- *Adding CRIS Label on PDF Documents*
- *CRIS Tips*

13.2 RESEARCH RECORD

There are some source documents (e.g., participant completed paper diaries or surveys, PK worksheets) that are not maintained in the medical record but still need to be maintained as source documents. Creating a research record is the easiest way to save these types of source documents. In the CCR, we need to keep these research records electronically which means the documents will need to be scanned and saved on a secure shared drive. Refer to CCR SOP ADCR-8 *Certifying Scanned Paper Documents.*

13.3 GENERAL DOCUMENTATION PRINCIPLES

Research source documentation is never by exception. Documentation that is acceptable in clinical practice may need additional details when the patient enters a clinical trial. Research team documentation in the medical record is critical for providing details regarding a participant's research study involvement, including education throughout the course of their study participation. This is also a part of ongoing informed consent. Documentation should be attributable, legible, contemporaneous, original, accurate and complete (ALCOA-C).

Encounters must be documented in a structured note in CRIS within 24 hours of any inpatient encounter and 3 calendar days for outpatient encounters including phone calls/emails.

If there is any conflicting, discrepant, or missing documentation, there must be a note in CRIS to address this from any licensed practitioner.

Documentation categories include but are not limited to:

- Past medical history/Prior therapies
- Concomitant medications/Measures
- Eligibility
- Informed Consent (See Section 12)
- Baseline symptoms
- Scheduled study visit details, including any protocol-specific activities completed such as biopsies, surveys, research bloods
- Clinical laboratory review, noting which labs are clinically significant or not
- Study drug administration
- Adverse events (See Section 15)
- Unscheduled visits
- Study status changes, including enrollment, off treatment and off study events
- Telephone calls and emails

For more information regarding documentation requirements refer to CCR SOP PM-3 *Clinical Research Documentation*.

13.4 SELF-ADMINISTERED STUDY MEDICATION

Self-administered study medications are prescribed in CRIS and dispensed by the outpatient pharmacy to be taken at home. When the patient returns to the CC for next evaluation, the pill diary, if applicable, remaining pills, and empty containers are returned to the CRC. Review of these ensures compliance with the protocol and ensures confidence in study endpoints like adverse event attribution and study drug effectiveness. While the Investigational Management

Branch (IVMB) of the pharmacy will help to closely monitor the overall inventory for the study drug along with ordering, storage, handling, and dispensing, it is important to understand research team member roles in ensuring this.

13.4.1 DRUG ACCOUNTABILITY

While study drug accountability is ultimately the PI's responsibility, this task is often delegated to the CRC. Both unused medications and empty containers should be returned to the CRC. For protocols that requires the participant to take study medication at home, review the CCR SOP PM-8 *Conducting and Documenting Drug Accountability for Oral Investigational Products that are Self-Administered by Research Participants.* When returning medications to the pharmacy, it is helpful to keep a scanned copy of the *Patient Take-Home Investigation Product Return Form* with the completed drug diary, if applicable, in the research record. PCCs should not be involved in drug accountability or returning medication to the pharmacy as these activities are not in their scope of practice.

13.4.1.1 EVALUATION OF PATIENT ADHERENCE TO SELF-ADMINISTERED PROTOCOL AGENTS

One of the basic concepts of protocol compliance is clear documentation of when and how much study drug(s) the patient received. Patients are prescribed study medications in CRIS by the providers. Patients then pick up their medications in the outpatient pharmacy located in 1-4480.

Self-administered medications are documented by the patient in a diary (usually found in the appendix of the protocol). These are designed so that they can be printed and filled out by the patient. The diary, like the rest of the protocol, is approved by the IRB during the review process and cannot be altered.

When the patient presents for the next cycle in clinic, the patient returns their completed and signed old diary, the remaining pills, and the pill containers. To prepare for clinic, the CRC should have the next diary ready for the patient with the dose prescribed notated and the dates already entered for them.

The research team should take time to review the returned completed diary in clinic with the patient and confirm that no doses were missed. Note how much medication was prescribed and reconcile that with the diary and the returned amount of study drug. Documentation in CRIS is important. Any discrepancies between the amount of study drug expected to be returned and what was actually returned must be fully explained in the CRIS note. Also, review notes that the patient may have written about symptoms experienced. Example documentation:

> *Patient presents today March 29 for initiation of cycle 2. She was dispensed 28 days of study drug X on March 1. Per patient diary, she took 1 mg of study drug X from March 1-*

March 28 with no missed doses. She returned one empty pill container to clinic which was returned to pharmacy. Pill count is correct.

13.4.1.2 MAILING ORAL STUDY MEDICATION TO PATIENTS

If the sponsor will allow for oral medications to be mailed to patients, the CC Pharmacy will do this via FedEx. The CC pharmacy documents the tracking number under the meds tab in CRIS. A member of the research team should follow up with the patient to ensure they received the medication(s) and that there was nothing damaged.

If the protocol is sponsored by the NCI Division of Cancer Treatment and Diagnosis Cancer Therapy Evaluation Program (CTEP), please review the *Guidance for Shipment of Oral IND Agents to Clinical Trial Subjects on Clinical Trials Sponsored by the National Cancer Institute Cancer Therapy Evaluation Program*.

13.5 CHEMOTHERAPY/BIOTHERAPY PRESCRIBING AND DOCUMENTATION POLICY

The Clinical Center policy for safety prescribing chemotherapy/biotherapy agents was updated in August 2023 to clarify and narrow the focus.

This policy applies to those agents (both investigational and FDA-approved) given for:

- Treatment of a malignancy
- As part of a conditioning regimen prior to transplant or cellular therapy
- For the prevention and treatment of graft versus host disease

All patients must receive education on therapies and sign informed consent before each new treatment regimen.

Education includes:

- Potential long and short term side effects of therapy, including infertility risks
- Symptoms or side effects that require the patient to contact the healthcare provider or seek immediate attention
- Follow up plans including laboratory and provider visits, coordination of care activities, and instructions for rescheduling or canceling, as appropriate
- Contact information with availability and instructions on when and whom to call

All patient education must be documented. Education materials may include the informed consent document. Other examples of materials may be found on the pharmacy website.

Patients receiving investigational agents must be consented to the appropriate research protocol. If patients on a research protocol are receiving non-investigational chemotherapy/biotherapy agents, they do not need to sign an additional consent as long as the risks/benefits are already described in the protocol consent.

The Consent to Chemotherapy/Biotherapy form must be completed for all other non-investigational agents. This form can be completed via paper or in iMed.

Patients must be cleared for treatment **before** chemotherapy/biotherapy CRIS orders are entered. As part of clearing the patient for treatment, a treatment note must also be entered in CRIS. This note is important for patient safety, as it communicates the treatment plan, and serves as key research documentation as it demonstrates protocol compliance.

Chemo/Bio Treatment Note

	Prior to the first dose (full note)	Prior to subsequent doses (abbreviated note)
Administered per IRB approved protocol: Yes vs No	✓	
Protocol number	✓	✓
Cycle, week, and/or day as appropriate	✓	✓
Dose level, arm, cohort, and/or dose group	✓	
List of chemo/bio agents and corresponding doses in metric units (e.g., mg/m^2)*	✓	
Notation regarding deviations from regimen described in the research protocol/reference	✓	
Dose modification including dose holding, dose adjustment, discontinuation, or delay		✓
Notation that patient is cleared to proceed with treatment	✓	✓

*ONLY for regimens that are not part of an IRB approved protocol or included in the Chemo/Bio Library. For regimens that are part of IRB approved protocols or part of the Library, it is not necessary to list all of the agents as long as the regimen does not deviate from the protocol.

For more information refer to CC MAS policy M11-2 *Policy for Safe Prescribing of Chemotherapy/Biotherapy Agents for Malignancy, Conditioning and Graft vs. Host Disease*.

13.6 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Visit and review the CRIS Learning Resources website
2. Review the HIMD handbook
3. Complete Part 1 of the *Documentation and Document Management* online learning module
4. Read CCR SOP PM-3 *Clinical Research Documentation*

5. Read CCR SOP PM-8 *Conducting and Documenting Drug Accountability for Oral Investigational Products that are Self-Administered by Research Participants*
6. Read CCR SOP ADCR-8 *Certifying Scanned Paper Documents*

13.7 ADDITIONAL RESOURCES

1. DCRI Websites
    a. Main site: https://www.cc.nih.gov/dcri
    b. Learning Resources: https://cris.cc.nih.gov/learningresources.html
    c. Request for System Changes including Order Sets: https://cris.cc.nih.gov/systemchanges.html
2. CCR ORN's website Computer Corner page

14 ESSENTIAL DOCUMENTS

Essential documents are those documents that individually and collectively allow for the evaluation of study conduct and quality of the data produced. They demonstrate compliance of the investigator, sponsor and monitor with GCP and applicable regulations. ICH GCP E6(R2) Section 8 provides the guidance and contents of the essential documents. Essential documents may also be referred to as the Investigator Site File or the Regulatory File. In the CCR, every protocol (i.e., interventional and observational), will have a regulatory file. To learn more about essential documents, please refer to part 2 of the *Documentation and Document Management* online learning module.

14.1 ESSENTIAL DOCUMENTS MAINTENANCE

Essential documents can be maintained in a paper format which are stored in a binder(s) or stored electronically in an e-regulatory file on a shared drive or by using a software platform. Currently, CCR is using stored file on a shared drive. Access to a protocol's file folder will be granted by the PSO.

It is the PI who is ultimately responsible for maintenance of the files, but this is often delegated to other team members. In the CCR, this falls to the PSO Manager but several documents that the CRC maintains will need to be sent to the PSO Manger for uploading to the file. When using documents to support an SAE or lab reference ranges, make sure participant confidentiality is maintained by redacting/blacking out participant names and using the unique subject ID number. For more information on the regulatory file maintenance including responsibilities of the PI, CRC, and PSO, see CCR SOP PM-6 *Guidelines for Development and Maintenance of Regulatory Files/Binders*.

14.2 TYPES OF ESSENTIAL DOCUMENTS

The following items are considered essential documents and need to be included in the regulatory file for each protocol:

- Protocol and associated modifications: Initial protocol and ALL protocol specific modifications with documented IRB and sponsor approvals
- Informed Consent: ALL approved versions with documented IRB approval
- Continuing Reviews: Approvals from IRB and study completion/termination report
- Ancillary Reviews: All ancillary review approvals
- FDA Form 1572 for all IND Trials: ALL versions signed and dated
- Curricula Vitae: Demonstrates qualifications of ALL investigator and sub-investigators, study coordinators. All CVs should be updated every 3 eyras or as required by sponsor. CVs are signed using PIV card.
- Serious Adverse Events: Copies of ALL reports including documentation of receipt from IRB, sponsor, FDA, OBA, as applicable
- IND Safety Reports: Copies of ALL reports including documentation of receipt from IRB
- Additional IRB correspondence
- Sponsor correspondence
- IRB Membership list or other documentation to support compliance with IRB regulations
- Investigator Brochure (IB): ALL versions; also include copy of approved agent package insert
- Recruitment advertisements/letters: ALL advertisements, letters or other communications going to participants or potential participants including IRB approval
- Sponsor correspondence
- Laboratory certification (e.g., CLIA) and reference ranges
- Investigation production information (e.g., drug accountability records, invoices)
- Research Team training (e.g., human subjects protection, GCP, protocol and protocol modifications)
- Records related to biospecimen collection and shipping, if applicable
- Logs
    - Delegation of task log (see section 5.1.2)
    - Screening and enrollment log (see section 12.12)
    - Monitoring visit log (see section 18.2)
- Notes to File (see section 14.3 below)

Refer to CCR SOP PM-6 for more details.

14.3 NOTE TO FILE

When something unusual happens in a clinical study, often a note to file (NTF) is needed. The NTF is considered a source document and must be signed and dated by either the person writing the note or the person reviewing and/or validate the information in the document. The NTF can be used to:

- Explain the location of a study document when it is not filed in the expected location
- Explain a discrepancy, the action taken in response, and the method adopted to prevent similar discrepancies
- Clarify an instruction or direction regarding some activity that is required by the protocol but is not clearly explained in the protocol

However, please remember that a NTF is not a panacea for all things that have gone wrong and is NOT a replacement for a reportable event to the IRB.

A good note to file includes:

- Study Name and IRB #
- Subject ID (if applicable)
- Purpose of the Note to File
- Explanation, clarification, and/or description of corrective act

14.4 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete Part 2 of the *Documentation and Document Management* online learning module
2. Read CCR SOP PM-6 Guidelines for Development and Maintenance of Regulatory Files/Binders.

14.5 ADDITIONAL RESOURCES

1. ICH GCP E6(R2) Section 8

15 ADVERSE EVENTS

An adverse event is any unwanted sign (e.g., an abnormal laboratory finding), symptom, or disease that was not seen before the individual's research participation, or worsening of a baseline symptom, regardless of expectedness or relationship to the research. Assessment of AEs and their timely documentation is critical to ensure research participant safety and quality data. The purpose of AE monitoring is to:

- Identify events that may have immediate effect on the safety of the participant, and possibly other participants
- Inform investigators, regulators, and others of new and important information about these events
- Provide a summary of the adverse experiences to help develop the drug or treatment toxicity profile

To learn more about associated AE definitions, please refer to *Adverse Event Definitions* which is part 1 of the *Adverse Event* online learning module. Protocols may also contain these important definitions. See Appendix C for a comparison table of definitions from the Office for Human Research Protection (OHRP), the Food and Drug Administration (FDA), and the International Council on Harmonisation (ICH) *Guideline for Good Clinical Practice* (GCP).

15.1 AE ASSESSMENT AND DOCUMENTATION

There is both an art and science to assessing adverse events. All AEs need to be assessed and documented in CRIS. It is important to document the review of tests and procedures in CRIS. For example, a provider should document if an abnormal laboratory value is of clinical significance or not. To learn more about assessment and documentation, please refer to *AE Assessment and Documentation* which is part 2 of the *Adverse Event* online learning module.

The principal investigator (PI) is responsible for assessing AEs particularly the causality, or attribution, but may delegate that to other members on the research team.
Note, causality assessment should be done by the PI or another physician investigator, PA, or NP if delegated this research task. There are 5 steps involved with assessing an AE:

- Selecting the correct AE term from the CTCAE
- Determining the severity of the AE using CTCAE
- Determining the causality/attribution of the AE
- Identifying the expectedness of the AE (will be needed to determine if event is reportable to the sponsor or IRB)
- Determining if the outcome of the event is serious - See Appendix C for definition (will be needed to determine if event is reportable to the sponsor or IRB)

Understanding how to collect and solicit information about adverse events is crucial.

All AEs should be documented in CRIS, including any workup or treatment needed. A good progress note documenting an AE will contain:

- Date the AE began; include time with infusion reaction
- Description of the event so that the severity/grade can be assessed using CTCAE
- Treatment for the AE
    - Was a medication given for the adverse event?
    - Did the study drug need to be held and/or discontinued temporarily or permanently?
    - Did the study drug dose need to be reduced, delayed, or increased?
- Attribution of the AE
- Date(s) the AE improved or worsened (i.e., grade changed)
- Outcome
    - Is the AE resolved?

- Is AE still present with no treatment needed?
- Is AE still present, but treatment needed?
- Did AE require hospitalization?
- Did AE result in death?

15.1.1 DOSE LIMITING TOXICITIES

Most clinical trials conducted at the CCR are Phase I or Phase I/II. The primary objective of a phase I study is to determine the maximum tolerated dose (MTD) of a drug or biologic by evaluating safety and tolerability. The studies are designed to enroll patients at sequential dose levels unless a patient experiences a dose limiting toxicity (DLT).

DLTs are a subset of adverse events that occur in a specific time period after the initiation of protocol therapy. DLT criteria is study specific and should be clearly outlined in the protocol, including any caveats. CRCs, NPs, PAs and staff clinicians should be familiar with their protocol's DLT criteria and assist the PI with prompt identification of DLTs and following the appropriate protocol procedures for treatment, subsequent accrual and dosing, and protocol stopping rules, if applicable.

If a DLT also meets the definition of a serious adverse event (SAE), unanticipated problem (UP) or other reportable event, it will need to be reported to the Sponsor and/or IRB. All DLTs need to be captured on the adverse event case report form (CRF) in the clinical database.

For phase I studies, be aware there may be a form or review process that must be signed off and/or completed by the Sponsor to get approval to move up dose levels. Please contact the protocol's Sponsor for more details. For CCR-held INDs, OSRO requires completion of their Dose Escalation Determine Form – refer to OSRO's website for the form and FAQs.

15.2 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The purpose of the Common Terminology Criteria for Adverse Events (CTCAE) is to provide standards for the description and exchange of safety information in oncology clinical research. It is used to define protocol parameters (e.g., maximum tolerated dose and dose-limiting toxicity) and provide eligibility assessment and guidelines for dose modification. The CTCAE facilitates the evaluation of new cancer therapies and treatment modalities, and the comparison of safety profiles between interventions.

The precursor to CTCAE was developed by the NCI's Cancer Therapy Evaluation Program (CTEP) as CTC (Common Toxicity Criteria) in 1983 to aid in the documentation and analysis of adverse effects of chemotherapy. Since version 1, the tool has been expanded and adapted internationally by the oncology community. It was renamed to the Common Terminology Criteria for Adverse Events in 2006 and with the 4th version in May 2009, become harmonized

with *MedDRA®* terminology. For more information on MedDRA®, review part 2 of the *Adverse Event* online learning module and visit MedDRA website.

The oversight or core committee for CTCAE development is comprised of members from NCI, FDA, NCI networks, MedDRA MSSO, and pharmaceutical companies and are committed to periodic reviews and revisions of CTCAE. Major CTCAE version updates are anticipated to occur no more often than every two years. Each time a major version of CTCAE is released, it will be harmonized with the latest release of MedDRA®. The current version is 5.0. Current and recent past versions of the CTCAE can be found on CTEP's website. CCR staff can also download the free CTCAE app to phones or tablets which then offers search features.

15.2.1 HOW TO READ THE CTCAE

The CTCAE is set up in a table format with 26 MedDRA® SOCs (System, Organ, Class) listed alphabetically. Within each SOC, AE terms are listed alphabetically. Each AE term consists of a definition and 5 numerical grades each with a description of severity. Within the description of the grade, a semicolon (;) is read as an "or" statement and a single dash (-) indicates that grade is not available for the specific AE term. Some grade descriptions include two types of activities of daily living (ADL):

- Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Each SOC has an "Other, specify" option for reporting events not listed in CTCAE. Use the following general guidelines when assessing the severity of an AE that is not currently available (i.e., other):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

15.3 PATIENT-REPORTED OUTCOME (PRO)-CTCAE

Approximately 10% of the AE terms found in CTCAE are symptoms or subjective assessments that require the provider/research team to translate what the patient is describing to an appropriate CTCAE term. These types of AEs are often referred to as patient reported outcomes (PROs) and are best rated by the patient. In 2008, the NCI's PRO-CTCAE project began with the goal of developing a valid, reliable, feasible and clinically useful patient version of the CTCAE for adults, adolescents and children participating in cancer clinical trials. PRO-CTCAE is a companion to the CTCAE. The symptoms used in PRO-CTCAE are also harmonized with MedDRA® terminology.

The PRO-CTCAE measurement system characterizes the AE based on frequency, severity, amount, interference, and presence/absence. The PRO-CTCAE Item Library includes 124 items representing 78 symptomatic events drawn from the CTCAE. PRO-CTCAE is currently available in more than 30 languages. A pediatric module permits self-reporting by children and adolescents ages 7-17 years. The Ped-PRO-CTCAE module is currently available in English, Simplified Chinese, and Italian. A version for caregiver reporting is available for use when children or adolescents ages 7-17 are unable to self-report. The pediatric module includes 130 items representing 62 symptomatic events drawn from the CTCAE. For more information on the PRO-CTCAE Measurement System, visit their website.

15.4 RECORDING OF AES

Recording of the AEs (i.e., data abstraction) onto a case report form (CRF) is dependent on the protocol. The protocol should clearly outline what AEs will be recorded. For some protocols, such as phase 1 studies, all AEs will be recorded. For others, maybe only grade 2–5 events will be recorded.

Though AE CRFs vary from sponsor to sponsor, most forms contain the following common elements:

- Description of the event
- AE term and severity using CTCAE
- Date the AE began
- Treatment for the AE
- Attribution of the AE
- Date the AE resolved.

Always refer to the protocol for recording exceptions and the CRF instruction manual for additional information on AE recording.

15.5 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete Parts 1 and 2 of the *Adverse Event* online learning module
2. Review your protocol(s) definition of a dose limiting toxicity (DLT), if applicable. How are these defined, managed and reported?

16 EXPEDITED REPORTING OF ADVERSE EVENTS AND OTHER EVENTS

16.1 EXPEDITED REPORTING OF AES FOR IND/IDE TRIALS

All investigators on a protocol need to understand what AEs must be reported to the IND/IDE sponsor in an expedited manner. Though the PI is ultimately responsible for this, CRCs are often the ones delegated to submit these AEs, though this task can also be delegated to other providers who serve as Associate Investigators (AIs). Knowing what to report, when, and to whom can be overwhelming because the clock starts ticking the moment the PI or another member of the team is made aware of the event. If another member of the team is notified before the PI, that team member should immediately notify the PI unless they have been delegated PI responsibilities. It can be helpful to review previous SAE reports in the regulatory file to get an idea of what is to be reported and how. Additional resources include colleagues, team leads, and staff from the Office of Education and Compliance who can help discern what needs to be reported and how to report it.

16.1.1 ADVERSE EVENT REPORTING CONDUCTED UNDER AN IND

Per the FDA IND regulations (21 Part 312.64), all serious adverse events (SAEs) need to be reported to the sponsor "immediately," regardless of attribution or expectedness. Most sponsors require a 24-hour timeframe. Research teams need to have a plan in place to meet this reporting deadline, particularly on holidays and weekends as CRCs are not on call. Late reporting of an SAE is a protocol deviation and may be cited during an FDA inspection.

As a reminder, an SAE is defined as the outcome of an AE:

- Death
- A life-threatening adverse event (i.e., the occurrence places the patient at risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event: outcome didn't result in death, be life-threatening, or require hospitalization but based upon appropriate medical judgment, they may jeopardize the research participant and may require medical or surgical intervention to prevent a death, life threatening event or hospitalization.

Sponsors may have different ways for reporting an SAE, so research teams will need to know how each sponsor is to receive an SAE and to familiarize themselves with their form/database. Below are some examples of how to report an SAE to a sponsor:

1. Sponsor specific SAE form
    a. For CCR-held IND trials, the Office of Sponsor and Regulatory Oversight (ORSO) has a specific SAE form with instructions. Note: Frequently Asked Questions is a helpful tool to read before you begin a submission to OSRO.
2. FDA Mandatory MedWatch Form 3500a; instructions available.
3. SAE specific database
    a. For Cancer Therapy Evaluation Program (CTEP) sponsored trials, the CTEP Adverse Event Reporting System (CTEP-AERS) is used. See website for details. Note: the CTEP-AERS report should be printed to pdf for the regulatory file.

There are 2 final steps in the reporting process. First, ensure that the final report is sent to the protocol's data manager. They will need to make sure the same data is collected on the routine AE CRF. Second, send the final report to the assigned PSO manager for uploading into the regulatory file.

To learn more about expedited reporting of AEs for IND/IDE trials, please refer to *AE Reporting for IND and IDE Trials* which is part 3 of the *Adverse Event* learning module.

16.1.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

There may be additional adverse events that need to be reported in an expedited manner to the sponsor that are not SAEs but could be of scientific or medical concern for the development of the IND product. These are referred to as adverse events of special interest (AESI). For example: an IND protocol may require all bleeding adverse events to be reported even if they are not an SAE. The reporting mechanism is the same as for an SAE.

16.2 IND SAFETY REPORTS

The sponsor is to notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug/biologic under its INDs or under any investigator-held IND) of the potential serious risks from clinical trials or any other source including:

- All serious and unexpected suspected adverse reaction (SUSAR)
- Findings from animal or in vitro testing
- Findings from other studies
- Increased rate of occurrence of serious suspected adverse reactions

This is communicated in writing as soon as possible, but no later than 15 calendar days after the sponsor's initial receipt of the information. These reports are referred to as IND safety reports (ISRs).

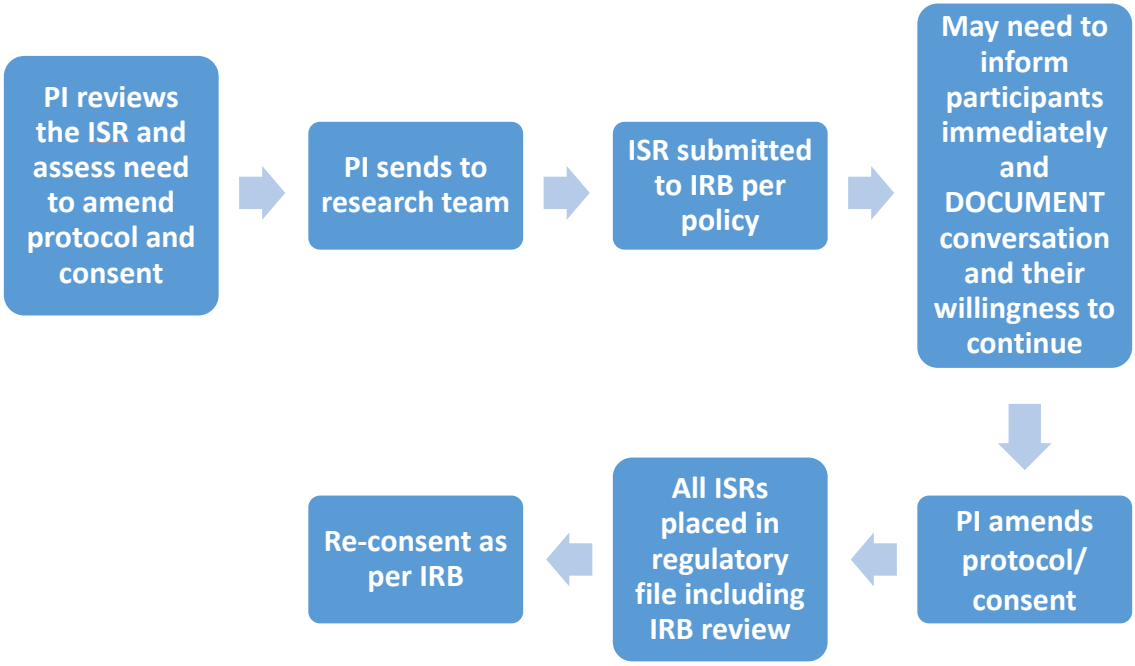
In addition to the ISR, the sponsor must notify FDA of any unexpected fatal or life-threatening suspected adverse reaction (SAR) as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The initial contact is by phone or email with a written follow-up report.

The FDA allows for various formats for the written report including:

- General narrative summary for ISRs that include overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies.
- FDA MedWatch Form 3500a, mandatory reporting form, which is the most common format, located on the FDA forms website.
- Council for International Organizations of Medical Sciences (CIOMS) I Form, which is used with international studies.

The sponsor's report to the FDA will include all previously submitted ISRs for similar SARs and analyze the significance of the SAR in light of previous, similar reports, or any other relevant information. Many sponsors will send many SAE reports that don't meet the criteria to be an ISR; however, a "true" ISR will result in a protocol modification.

The figure below describes what the investigator should do with an ISR.



16.3 EXPEDITED REPORTING TO THE IRB – REPORTABLE NEW INFORMATION (RNI)

The following events require expedited reporting to the NIH IRB per Policy 801 – *Reporting Research Events*. The CRC, PI and/or other designated member of the research team reports these events in PROTECT via the Reportable New Information (RNI) form:

- Non-compliance: Failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.
- Major protocol deviation: Deviation from the IRB-approved protocol that has, or may have the potential to negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- New information that might affect a participant's willingness to enroll or remain in the study. Examples include, but are not limited to:
-
    - An interim analysis that indicates a new risk or decreased effectiveness of the study intervention such that acceptability of risk is impacted
    - Withdrawal, restriction or modification of marketing approval of a drug, device or biologic used in the research
    - Publication in the literature or new marketing approval of a drug or device shown to be effective for the condition under study

- Complaint: Complaint of a subject that cannot be resolved by the research team.
- Death of a subject deemed to be at least possibly due to the research.
- Unanticipated Problem involving risks to subjects or others
- Audit: Audit, inspection, or inquiry by a federal agency.
- Confidentiality: Breach of confidentiality
- Unreviewed change: Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
- Incarceration: Incarceration of a subject in a study not approved by IRB to involve prisoners.
- Suspension: Premature suspension or termination of the research by the sponsor, investigator, or institution.
- Use of short form consent and rationale (see section 12.8.4)

Research teams should report any new information about a study as soon as they become aware of it.

Per NIH Policy 801 the following deadlines must be followed:

- Deaths that are possibly, probably, or definitely related to the research must be reported within 24 hours of any research team member awareness

- 7 calendar days for: non-compliance, major deviations, new information that might affect a participant's willingness to enroll or remain in the study, UP, short form use, and suspension

For more information see:

- M2P2 #8 *When do I submit a Reportable New Information (RNI) form to the IRB and what happens after the submission?*
- Tips & Tricks: Preparing Reportable New Information Forms
- NIH Investigator Seminar Series: *What Investigators Need to Know About Reporting Research Related Events* (Video - 60 minutes)

If the NIH IRB is the IRB of record, a site must follow the NIH IRB reporting requirements. If the study has an external IRB, the research team must follow their reporting requirements. However, if an event happens with a participant enrolled at an NIH site, or the event directly impacts the NIH site, the research team must also submit an RNI form in PROTECT. These events must be double reported because NIH has an institutional responsibility to know what is going on with its participants.

16.3.1 PROTOCOL DEVIATION TRACKING SYSTEM (PDTS)

A deviation is any change, divergence, or departure from the IRB-approved protocol. Tracking deviations is important for protecting our research participants and maintaining data integrity. In the CCR, research teams track deviations via entries in the Protocol Deviation and Tracking System (PDTS). See the PDTS User Guide for more information.

All major and minor deviations must be entered in PDTS. The PI must determine whether a deviation is major or minor, but the CRC usually enters in PDTS.

Major Deviation	Minor Deviation
Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.	Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study. ***Note:*** *A series of minor deviations pointing toward a more global issue that could affect the rights, safety or welfare of the participant or affect the validity of the study should be reported as a major deviation.*

The Office of Education and Compliance (OEC) tracks PDTS submissions and will contact the submitter with any questions or suggested revisions. **Note that entering a deviation in PDTS does not replace any required expedited reporting to IRB and/or Sponsor.**

CRCs may run deviation reports by protocol for a variety of purposes, including summarizing at the time of continuing review (see section 10.4) and in preparation for monitoring visits (see section 18.2).

For CCR-held IND studies, OSRO has additional reporting requirements classified as non-adherence. Non-adherence is defined as noncompliance with the clinical trial protocol, GCP, or protocol procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support to the clinical trial. Examples of this include missing protocol or protocol specific modification training. Non-adherence is also tracked in PDTS.

16.4 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete Parts 3 and 4 of the *Adverse Event* online learning module

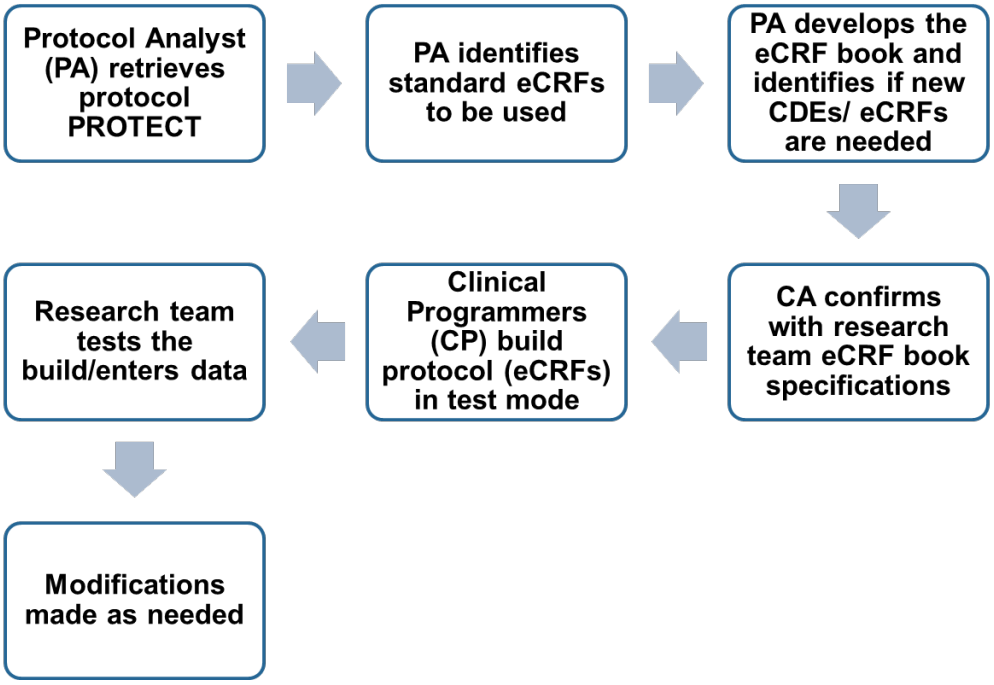
17 CLINICAL DATA MANAGEMENT

Clinical data management is a multidisciplinary activity that consists of various activities involving the handling of data or information that is outlined in the protocol to be collected and analyzed. While the PI is ultimately responsible for ensuring data integrity, everyone on a research team plays a role in maintaining quality data. Research team responsibilities for data management include:

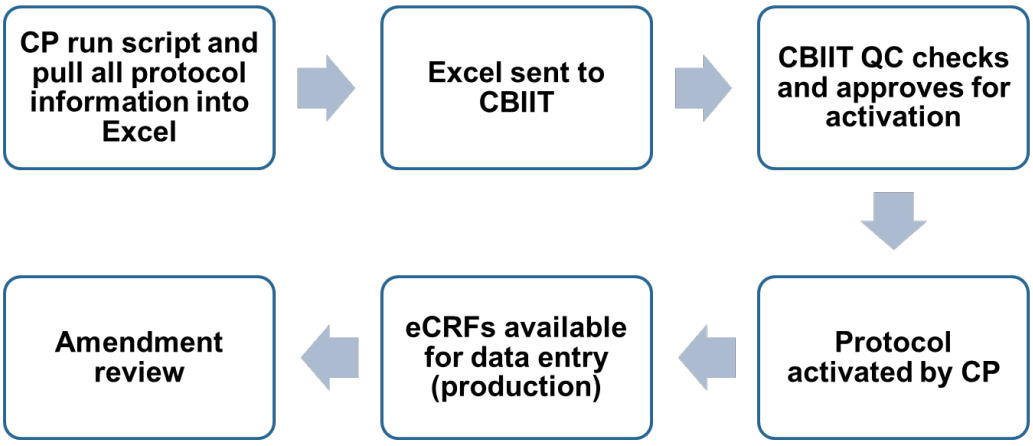
- Ensuring that all source data is documented in the Medical Record/Research Chart with accuracy, completeness, and consistency
- Ensuring the overall quality of the research data is verifiable and acceptable for sponsor submissions, publications, etc.
- Reviewing data discrepancies/clarifications for accuracy, consistency and timely response

The CRC helps develop, implement, and maintain a team quality control (QC) plan. This should include establishing a regular schedule of QC activities such as quality checking source documentation and case report form (CRF) completion.

PIs, CRCs, and data managers play an important role in database builds for new protocols for observational trials and CCR-held INDs. The build process typically looks like this:



There is a modified process for modifications that impact case report forms/database build.



PIs, CRCs and data managers should work together to review all electronic case report forms (eCRFs) and fields, making sure that the build only contains all of the needed fields and only the needed fields. It is important to delete anything extraneous, because if there is a field, the expectation is that it will be filled.

For CCR-held INDs, OSRO needs to review and approve eCRFs prior to activating the clinical site.

If there is a protocol amendment/modification that would require a database update, the CRC should proactively reach out to the IT team to initiate the update. See M2P2 #74 *What should you do if you have a protocol modification/amendment that impacts one of CCR's databases?* For industry and CTEP sponsored studies, the research team role may be more limited in database builds and updates, though feedback and questions should be welcomed.

17.1 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete the *Clinical Data Management* online learning module

18 MONITORING AND AUDITING

Quality management (QM) in clinical research encompasses both monitoring and auditing activities. QM is a multi-disciplinary activity that occurs throughout the protocol's life cycle. Ultimately, quality management in clinical research is Good Clinical Practice (GCP). GCP is the standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides quality data and ensures the rights and well-being of the research participants are protected. Compliance with GCP provides the public with the assurance that the rights, safety and welfare of the subjects are protected and respected and that the data generate by the research study is accurate, verifiable and reproducible. Monitoring and auditing activities in clinical research help to ensure this.

Monitoring is a QM function where study conduct is routinely assessed on an on-going basis at every step of the trial. During a monitoring visit, all aspects of the study at a specific site will be reviewed including informed consent processes, eligibility criteria, protocol compliance and that the data accuracy is supported or verified by source documents.

Auditing is also a QM function which involves an independent, systematic evaluation of a study's processes. Audits are not done continuously the way that monitoring is performed during a study, but instead are compliance snapshots in time. Auditors may look at study design, site/data management, statistical analysis and the Clinical Study Report. In general, auditors evaluate compliance to recognized standards (e.g., Code of Federal Regulations, International Council on Harmonisation, and site specific Standard Operating Procedures).

To learn more about monitoring and auditing, please refer to Part 1 of the *Monitoring and Auditing in Clinical Trials* online learning module.

As part of an overall CCR Quality Management plan, the Office of the Clinical Director (OCD) must be notified of monitoring and audit visits, as well as subsequent monitoring/audit visit reports. If the visit report requires action by the research team, that visit report response must also be forwarded to the CCR OCD. Communications regarding monitoring/audit visits (e.g., confirmation letters, reports, responses) must be filed in the protocol electronic regulatory file.

18.1 TYPES OF MONITORING VISITS

18.1.1 PRE-QUALIFICATION OR SITE QUALIFICATION VISIT

A pre-qualification or a site qualification visit is conducted by a sponsor representative to determine or ensure that a research site is fully capable and equipped to conduct a specific clinical trial. There may be a site assessment questionnaire that is sent by the sponsor even before the qualification visit. Questionnaires can include:

- Name and location of where the study is being conducted
- PI's previous experience in clinical research including phases of studies, the study population, the test article or similar product
- Study coordinator's previous experience in clinical research including phases of studies, the study population, the test article or similar product
- PI's current protocol portfolio and numbers and types of site staff supporting the PI
- Questions related to prior inspections by a regulatory agency
- Availability of targeted study population
- Language spoken by the targeted participants
- Location of source documents
- Adequate examination/procedure room space to conduct assessments as specified in the protocol
- Location of site SOPs
- Adequate laboratory space and equipment to conduct clinical and correlatives labs and if the equipment is properly maintained
- Information related to collection of specimens and chain of custody
- Adequate storage for test article (i.e., investigation drug, biologic, device) in accordance with the protocol, GCP, laws and regulations

When the qualification visit is scheduled in person, the sponsor's staff will be meeting with the research team as well as inspecting the facilities (e.g., where participants will be treated, where biospecimens will be stored, where drug will be stored). It is important for the CRC to ensure that all the various areas that will be toured can accommodate the request and coordinate the timing of the tours.

If a remote visit will be conducted and the sponsor would like to visit the patient treatment areas, this will need to be coordinated with the NIH CC. Please refer to CCR SOP ADCR-1 *Sponsor Site Qualification Activities* for more details on the CCR process for site questionnaire completion and site visit.

18.1.2 SITE INITIATION VISIT (SIV)

A site initiation visit (SIV) is conducted by the IND/IDE sponsor prior to participant enrollment, after IRB/IEC approval, after all essential documents are in place and after supplies (e.g., drug, device) is received. The purpose of the visit is to ensure that the PI and site staff understand:

- Roles/responsibilities/regulatory obligations.
- Protocol procedures.
- CRF completion instruction review.
- Requirements for records management/retention.
- Drug handling requirements.
- Enrollment and consent procedures.
- Expedited AE reporting procedure.
- Patient recruitment resources.

This will help to identify potential problems/issues/concerns and solutions prior to participant enrollment.

18.1.3 INTERIM MONITORING/SITE MONITORING VISIT (IMV/SMV)

The purpose of an interim/routine monitoring visit is to verify that the rights, safety, and welfare of clinical trial participants are protected, that the data reported to sponsors are accurate, complete, and verifiable from the source documents, and that the conduct of the trial is in compliance with the IRB-approved protocol and applicable regulatory requirements. Data accuracy and integrity are monitored and/or audited by numerous entities, both internal and external. The frequency of the visits will depend on:

- Protocol complexity
- Disease being studied
- Rate of recruitment
- PI/staff experience
- Site performance
- Sponsor's SOPs

At the time of the visit, the Clinical Research Associate (i.e., the monitor) will review progress of a clinical study, ensure protocol adherence and regulatory compliance and accuracy of the data.

18.1.4 CLOSEOUT VISIT

The purpose of the closeout visit (COV) is to review all regulatory documents, drug accountability record forms (DARFs), record retention guidelines. The visit typically occurs when the study is complete, PI's obligations fulfilled, and all data has been retrieved, entered and database locked. For CCR-held IND protocols, please see the OSRO SOP *205-S04 Protocol Close-Out*.

18.2 MONITORING LOG

The monitoring log provides documentation at the site that the study was monitored and the frequency of monitoring. The monitor and designated site staff both sign/initial the log to verify

the date the monitor was present. For consecutive days, each day is entered separately. This log is maintained by the CRC.

18.3 VISIT PROCESS AT THE NIH

The Clinical Center (CC) Health Information Management Department (HIMD) is responsible for providing external auditors/monitors access to information in the NIH Electronic Health Record (CRIS) to conduct official auditing and/or study monitoring requirements per NIH institute regulations. These auditor/monitor accounts have restricted rights to only view medical information for patients who are assigned to their account. These accounts will have access to the NIH CC's Referring Clinician Portal website in order to conduct study monitoring and all activities performed through the Clinician Portal website will be tracked, monitored, and reviewed by HIMD.

On-site monitoring should be limited to those visits that require in-person pharmacy and/or research laboratory visits. On-site monitoring is no longer required to take place in HIMD as the monitor will use the Clinical Portal to access medical records. On-site visits can take place in a meeting room scheduled by the research team via "CC-CRC Hatfield Conference Rooms" in Global.

All monitoring and auditing visits will adhere to the Clinical Center (CC) Regulatory Audit Guidelines. A Curriculum Vitae (CV) for each industry monitor/auditor must be on file with the Medicolegal Section. The CV must be updated annually. In addition, the monitor/auditor must sign a Confidentiality Agreement prior to being allowed to access information in the electronic medical record (Clinical Research Information System [CRIS]). This agreement must be signed annually.

For remote monitoring, all information in CRIS is available via the Clinician Portal. Industry monitors/auditors are required to complete training "Information Security Awareness for New Hires" prior to accessing the Clinician Portal. Training is available on the Clinical Portal website.

The *Regulatory Audit Guide* was developed by Clinical Center Health Information Management Department to explain the requirements for scheduling and conducting regulatory audits for interested NIH employees, NIH-contract employees and external auditors/monitors. If you have questions or comments, please contact the Health Information Management Division (HIMD) in Building 10, Room B1L400, 301496-3331, 7:00 a.m. to 5:00 p.m., Monday through Friday (excluding Federal Holidays) for prompt assistance. They can also be reached by email at CC-HIMD Regulatory Audits.

18.4 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Complete Part 1 of the *Monitoring and Auditing in Clinical Trials* online learning module
2. Read CCR SOP PM-13 *Industry-Sponsored Studies Monitoring and Audit Visits*

3. Read CCR SOP PM-13a *Center for Cancer Research Sponsored Studies Monitoring and Audit Visits*
4. Read CCR SOP PM-13b *Monitoring and Audit Visits by ASRC (Artic Slope Regional Corporation)*
5. Read CCR SOP ADCR-1 *Sponsor Site Qualification Activities*

19 PROFESSIONAL DEVELOPMENT

Professional Development (PD) is essential for all research professionals. PD activities enhance our knowledge, skills, and performance. They include a variety of activities such as attending webinars or conferences, presentations, publications, and membership in professional research organizations. Knowing which professional organizations along with educational opportunities that are provided to you while you venture through your journey here in the CCR will enhance your professional development.

19.1 DEVELOPING AND MAINTAINING A CURRICULUM VITAE (CV) AND PROFESSIONAL DEVELOPMENT LOG

For those working in clinical research, it is important to know how to develop and update your Curriculum Vitae (CV) and your professional development log. The Office of Education and Compliance website has several slide sets available to assist in various professional development activities including:

- Developing & Maintaining Your Curriculum Vitae
- Abstract, Poster and Beyond
- Developing Your Presentation: Tips for Success
- Professional Portfolio for the Research Nurse

Click here to visit the website and learn more.

19.1.1 CURRICULUM VITAE

A CV provides a clear description of professional accomplishments and showcases knowledge, skills, and expertise. One important aspect of your professional development is ensuring that your CV is written in a format that will provide you with the most accurate depiction of your responsibilities in your role. In developing your CV, it is important to remember to have structured content in a manner that is understandable to professionals both within the research environment as well as others who may consider you for opportunities outside of research. Your position description (PD) is provided to you by your supervisor which can be used when developing/updating your CV. You will also be required to submit your CV to your PSO manager for your central regulatory file. On the main professional development website above, you will find a list of common CV headings and content and a CV checklist.

19.1.2 PROFESSIONAL DEVELOPMENT LOG

Another important aspect of professional development is maintaining your Professional Development Log. There are logs for nurses and non nurses, and the appropriate log should be downloaded and saved to your personal drive and kept in a folder that can be easily accessed to update the log in real time. It includes tracking continuing nursing education, continuing medical education, academic education, publications, presentations, precepting, and volunteer leadership services as completed throughout the year.

Reviewing your PD log at the time of your annual performance evaluation can help you identify your learning needs and what learning activities you attended or participated in. Below are the professional development activities offered in the CCR and the NIH IRP. You will learn about these activities via email from various CCR/IRB distribution lists.

19.2 PROFESSIONAL DEVELOPMENT ACTIVITIES

The complex and rapidly changing clinical research enterprise requires research professionals with advanced knowledge, skills, and competencies to meet the growing demands. Through professional development activities, you can reach your professional goals and at the same time meet the needs of a demanding and dynamic research environment. There are many opportunities to achieve continuing education. They are offered both in clinical education and in research, many awarding contact hours. Below are some of the routine offerings in the CCR and the NIH IRP.

19.2.1 ONCOLOGY LUNCH & LEARN

The Oncology Lunch & Learn sessions are a series of educational presentations developed to provide an open forum to discuss clinically focused topics in an informal, relaxed atmosphere. They are open to all in the CCR and offered monthly. The goal of the OLL sessions is to have attendees identify one new concept related to improving cancer care for patients. The sessions are 45-50 minutes followed by Q & A. Participants can enjoy a collegial environment in which to freely express their ideas, opinions, ask questions, share best practices, etc. The Oncology Lunch & Learn schedule along with past presentations is located on the Education and Training page. Nursing continuing professional development contact hours are awarded.

19.2.2 CCR CLINICAL RESEARCH FORUMS

The purpose of the CCR Clinical Research Forums is to provide a variety of research related presentations in an open setting which will facilitate interaction and dialog between research experts and research team members. It is the goal of the research forums to promote an awareness of research related issues, to increase understanding of specific issues and content areas, and to offer a mechanism for professional information dissemination and discussion. The clinical research forums are open to all in the CCR and offered monthly. The CCR Clinical

Research Forum schedule along with past presentations is located on the Education and Training page. Nursing continuing professional development contact hours are awarded.

19.2.3 GRAND ROUNDS

There are four types of Grand Rounds offered routinely for CCR staff:

- CCR Grand Rounds: Offered weekly on Fridays from 12-1 PM. CCR Grand Rounds is a lecture series addressing current research in clinical and molecular oncology. Speakers are leading national and international researchers and clinicians.
- Oncology Nursing Grand Rounds: Offered twice annually. Provides a forum to strengthen nursing research and integrate nursing research into oncology nursing practice using an evidence-based practice framework.
- Clinical Center Grand Rounds: Offered weekly on Wednesdays from 12-1 PM via Webcast. Presentations are offered by senior NIH physicians, and the discussions focus on current topics in patient care and clinical investigation.
- Ethics Grand Rounds: The Department of Bioethics presents Ethics Grand Rounds as part of the Clinical Center Grand Rounds program. Ethics Grand Rounds generally take place four times per year and focus on clinical/clinical research ethical issues and concerns.

All sessions, except for Oncology Nursing Grand Rounds, offer CMEs through Johns Hopkins School of Medicine Office of CME. See the session disclosure for information. For Oncology Nursing Grand rounds, nursing continuing professional development contact hours are awarded.

19.2.4 OTHER ACTIVITIES

In lieu of in-services, informal learning activities are available including Monday Morning Practice Pearls and Q & A sessions.

19.2.4.1 MONDAY MORNING PRACTICE PEARLS (M2P2)

Monday Morning Practice Pearls answer a question that has been posed from staff to clarify, update, or share new information. They can be found on the Education and Training page.

19.2.4.2 Q & A SESSIONS

Q & A sessions allow staff to pose questions about topics of interest. The often focus on information related to changes in policies and/or regulations. These sessions will be announced via an email to staff.

19.3 PROFESSIONAL PORTFOLIO

A professional portfolio is a personalized collection of documents that demonstrate an individual's knowledge and skills over time as well as a tool used to document professional competency. It encompasses a reflection of you in your professional career, a record of your professional development, proof of performance on the job, evidence of your learning and mastering new skills, and tangible evidence of what you have accomplished. Your portfolio should include your CV, documentation of professional education including professional licenses, professional certifications, transcripts, diplomas, and continuing education certificates. Your portfolio should also contain your publications, documents verifying your presentations, honors, awards, and special achievements. It should document your professional experience and expertise which may include your performance evaluations, letters of recommendation, letter from your supervisor, thank-you's/accolades, case studies/exemplars and membership cards. It is recommended to keep your portfolio concise, neat, honest, and up to date.

19.4 PROFESSIONAL ORGANIZATIONS

There are many professional organizations either disease specific or research focused that offer educational and leadership opportunities. Below are the main groups.

19.4.1 FOR ANY CLINICAL RESEARCH PROFESSIONAL

19.4.1.1 ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS (ACRP)

The Association of Clinical Research Professionals (ACRP) was founded in 1976 and supports clinical research professionals. ACRP offers 4 types of research specific certifications based on your role. There are many live educational programs as well as online courses and webinars to participate in when looking for continuing education offerings. ACRP's annual meeting is held in April.

19.4.1.2 SOCIETY OF CLINICAL RESEARCH ASSOCIATES (SOCRA)

The Society of Clinical Research Associates (SOCRA) was established in 1991 and encompasses professionals who are in the clinical research field and have a role of conducting clinical research trials. SoCRA offers one certification program, the certified clinical research professional (CCRP®). There are many live educational programs as well as online courses and webinars to participate in when looking for continuing education offerings. SoCRA's annual meeting is held in September.

19.4.2 FOR NURSES

19.4.2.1 ONCOLOGY NURSING SOCIETY (ONS)

The Oncology Nursing Society (ONS), is a national organization created after the 1973 National Cancer Nursing Research Conference and was incorporated in 1975. Founded to support the oncology nursing profession, ONS is considered a valuable oncology nursing resource. There are currently over 35,000 members throughout United States and internationally. ONS benefits nurses via many different avenues to obtain various CEs through offerings of online courses, journal articles, podcasts, etc. ONS Congress, the annual meeting, is offered in the spring, late April/Early May.

19.4.2.2 INTERNATIONAL ASSOCIATION OF CLINICAL RESEARCH NURSES (IACRN)

The International Association of Clinical Research Nurses (IACRN) was founded in 2009. The Association's purpose is to define, validate and advance clinical research nursing as a specialty practice and to support the professional development of registered nurses who directly or indirectly impact the care of clinical research participants. The organization will help provide you with an avenue to further educate yourself in research and what a research nurse's role is in caring for the research participants as well as conducting clinical trials, maintaining the integrity of the protocol and regulatory aspects of clinical trials. IACRN's annual conference is held in October.

19.5 RECOMMENDED ACTIVITIES FOR NEW STAFF

1. Develop or revise existing CV to include current role
2. Start a professional development log

19.6 ADDITIONAL RESOURCES

- CCR Education and Training website

20 APPENDICES

20.1 APPENDIX A: LANGUAGE INTERPRETIVE PHONE SERVICES

The language interpretive phone service is useful for staff when there is a need to contact patients that speak other languages to discuss protocol specifics, scheduling appointments or gathering other useful information regarding the patient.

NIH uses CyraCom, a healthcare-specific translation service using certified interpreters to dial in and translate between NIH staff and patients. This is an excellent tool to utilize. Please read the following in order how to place a call using CyraCom and how to use if you should receive a call from a patient for which you do not speak the language for.

Placing Outbound Calls:

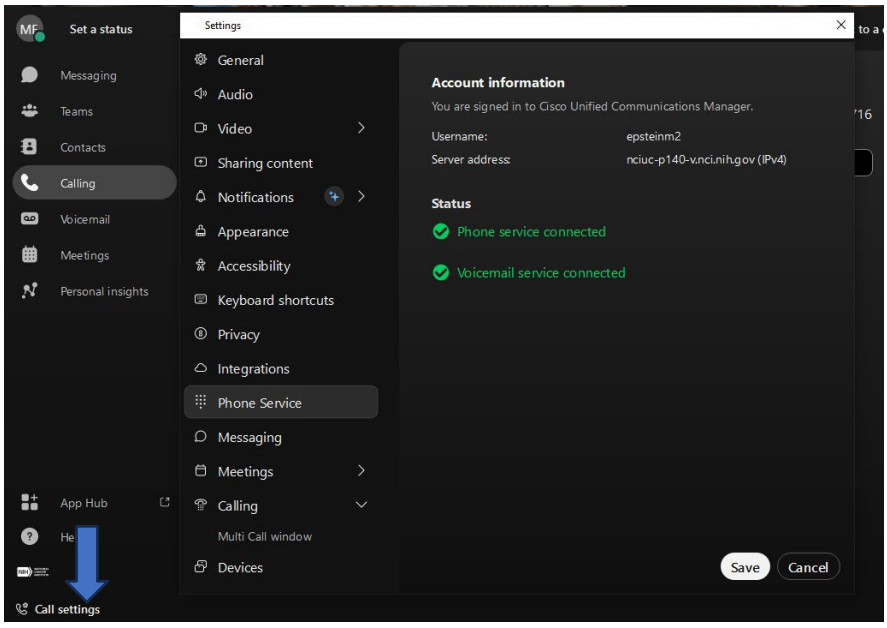
1. Dial **1-800-481-3293** (dial 9 before 1 if required)
2. Enter account number (**501013226**)
3. Enter pin account (**0977**)
4. State Language preference
5. Confirm language
6. When prompted, add a person if required follow command
7. Domestic call: Press # 1, International Call: Press #2
8. Enter desire phone number (delay will occur)
9. Once interpreter arrive online state:
    a. Your name, job title, and institution
    b. Name of the person you are calling
    c. Purpose of the call (short and concise sentences)
    d. Request to leave a message if there is no answer

Receiving Inbound Calls:

1. Ask person to hold
2. Press transfer or conference button
3. Listen for dial tone, patient will be placed on hold automatically
4. Dial **1-800-481-3293** (dial 9 before 1 if required)
5. Enter pin account (**0977**)
6. State Language preference
7. Confirm language
8. Confirm if another person needs to be added to the line
9. Next Available Interpreter will come on the line & greet you
10. Inform the Interpreter you will be conferencing in a person
11. Press transfer/conference button & all parties will be connected

20.2 APPENDIX B: INTERNATIONAL CALLING TIPS USING WEBEX

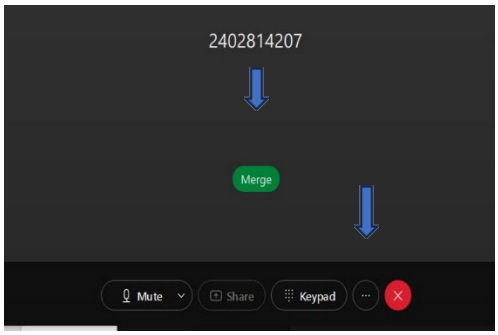
- Open WebEx and make sure you are signed into phone services under call settings using NIH username and password.



- To dial an international number: you will dial a 9 + 011 + country code + region code + number. For example, if you were to call to find out the automated time/temperature in Australia, the number to call would be 9-011-613-966-94916. If you do not have a country code, Google can help.

If using an interpreter through language line or NIH:

- If using the interpreter line start by calling 1-800-481-3293 account number is 501013226 pin0977 (interpreter line cannot call an international number) then click the ellipsis and choose “Conference”. A new keypad will appear, type in the international number. Once the patient answers click merge to merge calls with interpreter. If using an NIH interpreter, use the same technique with the interpreter’s phone number called first.



20.3 APPENDIX C: COMPARISON OF AE TERMINOLOGY

Comparison of Adverse Event Terminology Among Regulatory Bodies			
Term	**United States Office for Human Research Protections (OHRP)[1]**	**United States Food and Drug Administration (FDA)**	**International Council on Harmonization (ICH)[4]**
Adverse Event (AE)	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, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice). Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. [2]	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product
Serious Adverse Event (SAE)	Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria: • results in death; • is life-threatening (places the subject at immediate risk of death from the event as it occurred); • requires inpatient hospitalization or prolongation of existing hospitalization; • results in a persistent or significant disability/incapacity;	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require	Any untoward medical occurrence that at any dose: • results in death, • is life-threatening, • requires inpatient hospitalization or prolongation of existing hospitalization, • results in persistent or significant disability/incapacity, or • is a congenital anomaly/birth defect.

	• results in a congenital anomaly/birth defect; or • any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition	hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [2]	
Life threatening	See Serious Adverse Event definition above	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. [2]	N/A
Unexpected	Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either: 1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or 2. the expected natural progression of any underlying disease, disorder, or condition of	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.[2]	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

	the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.		
Suspected Adverse Reaction (SAR)	N/A	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. [2]	N/A

[1] Office for Human Research Protections. (2007, January 15). *Guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse events*. Retrieved from http://www.hhs.gov/ohrp/policy/advevntguid.html

[2] IND Safety Reporting, 21 C.F.R. 312.32 (2023). Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

[3] U.S. Food and Drug Administration. (2009, January). *Guidance for clinical investigators, sponsors, and IRBs: Adverse event reporting to IRBs—Improving human subject protection*. Retrieved from https://www.fda.gov/media/72267/download

[4] International Council on Harmonisation of Technical Requirements for Registrations of Pharmaceuticals for Human Use (2016, November 9). *Guidelines for Good Clinical Practice E6(R2).* Retrieved from https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf