CLINICAL RESEARCH COORDINATOR ORIENTATION AND RESOURCE MANUAL

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1 WELCOME AND INTRODUCTION FOR CLINICAL RESEARCH COORDINATORS

Welcome to the Office of Research Nursing (ORN) in the Center for Cancer Research (CCR)! Whether you are a federal employee or a contractor, nurse, or non-nurse, we are excited to have you join our team. The orientation and educational needs of our clinical research coordinators are complex due the level of knowledge necessary to fulfill the role at a professional level. Responsibilities include the interacting with patients and their families as well as the planning, coordination, and administrative aspects of the clinical research protocol itself.

This manual was developed as a central resource to support our clinical research coordinators (CRC). It will help guide you through the complexities of the role, identify required activities for clinical research coordinators new to the CCR, and serve as a resource for current research clinical research coordinators. Each section of the manual includes section content and additional resources as well as required activities for new hires.

1.1 NURSES IN THE CRC ROLE

Nurses have been involved in the CRC role for decades. Two professional nursing associations have recognized this role and defined scope and standards of practice and competencies.

In 2007, the Oncology Nursing Society (ONS) working in collaboration with the Clinical Trials Nurse Special Interest Group began the process of developing competencies for the oncology nurse who is in the CRN Study Coordinator role. The first set of competencies was published in 2010 with a revision in 2016. Your performance is evaluated based on the 2016 competencies. Your ORN team lead will review these with you.

In 2009, the International Association of Clinical Research Nurses was established. In 2016, the American Nurses Association recognized the specialty practice of clinical research nursing. As defined in the Scope and Standards of Practice (2016), clinical research nursing is defined as the:

> "specialized practice of professional nursing focused on maintaining the equilibrium between care of the research participant and fidelity to the research protocol."

One of the roles of the CRN is that of the CRN Study Coordinator. This is your role!

To learn more about the history of clinical research nursing and the oncology clinical trials nurse, please read the following article:

> Ness E. (2020). The Oncology Clinical Research Nurse Study Co-Ordinator: Past, Present, and Future. *Asia Pacific Journal of Oncology Nursing, 7*(3), 237-42. doi: 10.4103/apjon.apjon_10_20

2 INTRODUCTION TO THE NIH, NCI, AND CCR

2.1 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 Acting Director is Dr. Lawrence A. Tabak. 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.

2.1.1 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 constitute 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.

2.1.2 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, Children's School, 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
- Chief Scientific Officer: John Gallin, MD
- Chief Medical Officer: Colleen Hadigan, MD, MPH
- Chief Financial Officer: Pius A. Aiyelawo, FACHE (acting)
- Chief Nurse Officer: Barbara Jordan, DNP, RN (acting)
- Patient Representative: Antoinette (Toni) Jones, MSOD, RN

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

2.1.3 OFFICE OF HUMAN SUBJECTS RESEARH 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.

2.2 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 Director is Dr. Monica Bertagnolli. 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/.

2.3 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 Director of the CCR is Dr. Tom Misteli. There are 2 scientific directors that assist Dr. Misteli - one for basic research and the other for clinical research. Dr. Glenn Merlino is the Scientific Director for Basic Clinical Research and Dr. Tom Misteli is also the Acting Scientific Director for Clinical Research. 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.

2.4 OFFICE OF THE CLINICAL DIRECTOR (OCD)

Each I/C in the 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 Acting Clinical Director for CCR, Dr. James Gulley, oversees and assures the quality of medical care delivered to patients treated on CCR clinical trials. The Deputy Clinical Director is Cheryl Royce. 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.

2.4.1 OFFICE OF RESEARCH NURSING (ORN)

The Office of Research Nursing (ORN) 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.

2.4.2 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 monitoring visits and FDA inspections
  - Providing consultative services related to clinical research

2.4.3 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)

2.4.4 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.

2.4.5 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.

2.4.6 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.

2.4.7 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)

2.5 REQUIRED ACTIVITY FOR NEW CRC HIRE

1. View video of NIH: https://www.youtube.com/watch?v=ezpi8J1UQA0 (4:52 minutes)
2. Bookmark the websites found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Important+Web+sites
3. For Nurse CRC, read the following:
   - Ness E. (2020). The Oncology Clinical Research Nurse Study Co-Ordinator: Past, Present, and Future. *Asia Pacific Journal of Oncology Nursing, 7*(3), 237-42. doi: 10.4103/apjon.apjon_10_20
   - Oncology Nursing Society. (2016). *2016 Oncology clinical trials nurse competencies*. Pittsburgh, PA: Author. Retrieved from

2.6 ADDITIONAL RESOURCES

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

3 ADMINISTRATIVE – HUMAN RESOUCES

Onboarding of new CRCs have many administrative steps.

3.1 CREDENTIALING FOR NURSE CRCS

It is the policy of the NIH CC Nursing Department (CCND) that all RNs who are not employed by the NIH CCND complete a credentials verification and privileges request process with privileges granted by the Chief Nurse Officer. The credentialing policy can be found at this link: http://intranet.cc.nih.gov/nursing/resources/cr_verification.html with required forms and training checklists to complete the credentialing process. As soon as you receive a start date, your Team Lead will send the following:

1. A copy of your Position Description (PD)
2. Demographics Information Sheet for Extra-Departmental Nurses/Institute Nurses
3. The letter of agreement.

Your Team Lead will ask you to complete and sign these forms. In addition to the forms above, you will be asked to email your Team Lead:

- Valid CPR card
- Copy of your current nursing license
- Updated signed and dated CV listing your new position in the ORN. You can use the PD to update your CV.

You will need to complete the trainings found at https://intranet.cc.nih.gov/sites/nihintranet/files/assets/owmd/pdf/CC_New_Employee_Training_Assessment_Record.pdf before you can be credentialed. Once you've completed the trainings, email your team lead the signed completed *Training Assessment Record for New Employees*. Your Team Lead will sign the checklist and include it in the credentialing paperwork. Please keep all certificates you receive for the web-based training for your records and send a copy to Tracy Kirby.

3.2 MANDATORY ORIENTATION ACTIVITIES

3.2.1 FEDERAL EMPLOYEES

The following orientation activities are required for all federal employees:

1. NIH Virtual Orientation: Occurs via Zoom on the first Monday of each pay period from 9:00 AM – 12:00 PM. The Zoom information will be sent before 3PM on that Friday before. Visit the Virtual NIH New Employee Orientation website. This site also has an onboarding checklist for you to follow.
2. NCI Orientation (NEO) is available in the HHS Learning Management System (LMS). All new NCI employees will receive an email from the Office of Workforce Planning and Development (OWPD) with information on how to register for NEO in LMS. This is required to be completed within the first 30 days of employment.

3.2.2 FEDERAL EMPLOYEES AND CONTRACTORS

The following orientation activities are required for all CRCs:

1. Clinical Center New Employee Orientation: All new employees working in the NIH Clinical Center, building 10, must complete initial training as part of their onboarding process. View more information and the list of required CC training courses.
2. CCR Clinical Trials Orientation Web Modules: All new employees must complete the **10 online modules** during the first 6 weeks of employment or prior to classroom orientation
3. Virtual Classroom Orientation**:** See the website activity number 22 for dates, times and agenda.
4. Study Coordinator Orientation: See the website activity number 22 for dates, times and agenda.
5. Electronic Health Record/CRIS Training: Team Lead in coordination with employee and employee's preceptor will schedule CRIS training as soon as new employee receives a start date or Entrance on Duty (EOD). Employee should take the training once scheduled. Employee will only receive access once training is completed and the employee is credentialed. View the CRIS Training Track Registration Walkthrough to

register for the nursing track. At the end of the short video, you will be taken to the correct track and register.

a. Required Nurse CRC CRIS training: Introduction to CRIS (first), Non-Prescriber Order Entry, Clinical Documentation, Worklist Manager.
b. For non-nurse CRC CRIS training: Introduction to CRIS (first), Clinical Documentation
c. Current NIH employees do not need to repeat CRIS training and Team lead will sign eCARF included in the credentialing application packet to prevent loss of CRIS access.

3.3 NIH ENTERPRISE DIRECTORY (NED)

The NIH Enterprise Directory (NED) is an electronic directory of people who work at the NIH. Note that for internal NIH candidates, ORN Administrative Officer (AO) initiates and accepts the transfer/re-assignment in NED to avoid employee being dropped from CRIS and Global.

It's important to update your personal information and work contact information in NED. Visit the NED Update Instructions website for more information.

3.4 EQUIPMENT

3.4.1 COMPUTERS

For internal NIH candidates, your Team Lead will coordinate with the ORN Administrative Support staff to order the IT equipment. For external candidates, your Team Lead will coordinate with the ORN Administrative Support staff to order the IT equipment once you are listed in NED. Team Lead will be included in all email correspondence relating to ordering of computer.

ORN Administrative Support staff will also place a Help Desk ticket and request the date for the technician to perform the initial set up. The request should include Adobe Acrobat Professional, CRIS, and MS Teams to be loaded on new computer.

Current NIH employees may not be able to obtain new physical equipment until the first day of employment with NCI. This may be delivered to the employee's home address, or it can be picked up onsite. For new NIH employees the computer may be mailed to home or can be picked up onsite. Your Team Lead will direct you on how to obtain a property pass for laptops and cell phone. It can be requested through the IT self-service website: https://myproperty.nih.gov/.

Your assigned preceptor will assist employee to request access to their team's shared drive, calendar, eFax, and distribution lists. If needed this may require an IT Help Desk ticket.

3.4.2 TELECOMMUNICATIONS

3.4.2.1 DESK PHONE

- VOIP phones follow the current NCI employee (will need a new phone if coming from another IC).
- If new equipment and number are required, the ORN Administrative Support staff will place an IT ticket request. You will be notified by email regarding phone number. ORN AO will update NED with new phone number. (COVID- if a physical phone is needed then a separate Help Desk Ticket will need to be placed).

3.4.2.2 CELL PHONE

- New phone: Supply monies for CRCs are with the Branches. Your Team Lead or the ORN Administrative Support staff will ask the Branch AO to order a new cell phone.
- Contractors: Leidos will supply cell phones for their employees. For Astrix/Kelly, the branch will order the cell phone
- The employee contacts NIH Pager Services (496-1211) to update their phone number/pager number and other hospital areas as applicable. The employee also needs to update this information in NED.

3.4.2.3 PAGER

There are 2 options:

1. For iPhone paging services (Spok mobile), you will need to place a request via the IT help desk to activate this service on your iPhone. When Spok mobile is activated, a pager # is assigned.
2. You can also have a physical pager. If you are inheriting a pager from another CRCs, just place an IT help desk request to change the former CRC's name to your name; you can request to keep the same pager # or have a different one. You can also submit an IT help desk request to link Spok mobile and physical pager #'s together.

3.5 INTEGRATED TIME AND ATTENDANCE SYSTEM (ITAS)

The NIH Integrated Time and Attendance System (ITAS) is the timekeeping tool used by all Federal employees to track working hours within the specific tour of duty. It is also used for submitting annual and sick leave requests, and for donating annual and sick leave hours to fellow Federal employees in need of extra hours.

Your Team Lead will work with the ORN AO to ensure that you are in ITAS prior to the end of the first pay period. Your team Lead will ensure the correct tour of duty and contact the ORN timekeeper for corrections. If the employee is a transfer within NIH and there are issues with the transfer of the employee's timecard, your Team Lead will contact the ORN AO to resolve with the employee's transferring Institute.

To learn more on how to request leave, verify your timecard, etc. see the ITAS User Manual. Your timecard needs to be verified by you before the end of each pay period. Check with your team lead when they need to have you verify your timecard. Here is a quick link to the Employee Actions page in the manual: https://hr.nih.gov/hr-systems/itas/user-guide/employee-actions. Use the *On This Page* navigation menu on the right side of the site to quickly navigate to various employee actions.

3.6 PERFORMANCE MANAGEMENT APPRAISAL PROGRAM (PMAP)

The Performance Management Appraisal Program (PMAP) is designed to communicate organizational goals and objectives between you and your supervisor. It runs on a calendar year cycle. PMAP is one component of the on-going process of performance management/ evaluation. PMAP evaluation implements a 5-tier rating system consisting of the following levels of performance:

- Achieved Outstanding Results (Level 5)
- Achieved More Than Expected Results (Level 4)
- Achieved Expected Results (Level 3)
- Partially Achieved Expected Results (Level 2)
- Achieved Unsatisfactory Results (Level 1).

The nurse CRC PMAP is based on the ONS CTN competencies. Your supervisor should review these with you and initiate your electronic PMAP within the first 30 days of hire whether you are a new hire to NIH or a transfer. Make sure you review your PMAP to understand how you will be evaluated. All PMAPs are done electronically at ePMAP.

A midyear ePMAP will need to be completed for employees whose EOD is after the beginning of the year through November 15 of the current year. The AO is responsible for tracking the midpoint between the time of the employee EOD and end of the appraisal period to remind the employee and supervisor to conduct midyear at that time.

3.7 SISWEB

To be developed

3.8 REQUIRED ACTIVITY FOR NEW CRC HIRE

1. For Nurse CRC: Complete the CCND credential verification process
2. Complete CRIS training
3. Complete NIH New Employee Orientation (federal employees only)
4. Complete NCI Orientation (federal employees only)
5. Complete CC Orientation
6. Complete the CCR Clinical Trials Orientation Web Modules (10 modules)

7. Attend CCR Clinical Trials Orientation
8. Attend CCR Study Coordinator Orientation
9. Complete set up computer, phone, and pager, if applicable
10. Confirm information in NED is correct
11. Federal CRC: Confirm access to ITAS (federal employee only)
12. Federal CRC: Sign on to your initial ePMAP (federal employee only)

3.9 ADDITIONAL RESOURCES

- 430-1: Performance Management Appraisal Program (PAP) Policy

4 ADMINISTRATIVE – CLINICAL RESEARCH

4.1 ADMISSIONS TO THE NIH CLINICAL CENTER

To be developed

4.2 EXTERNAL LOCATION (EXT LOC) REQUIREMENTS

The NIH Clinical Center (CC) has created a process for registering patients who are participating on 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 to the CC for consultation; and/or specimens sent to DLM, DTM or Anatomic Pathology for testing.

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. The forms are required for registering these types of patients include:

- EXT-LOC Registration Consent
- EXT-LOC Consent-Authorization for Electronic Communications
- EXT-LOC Notice and Acknowledgement of Info Practices
- Research Participant Registration EXT-LOC Demographics Form

These forms as well as instructions for submitting the EXT LOC ATV request and signing the 2 above noted consents can be found on the HIMD website at: https://intranet.cc.nih.gov/medicalrecords/ext-loc/index. 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*.

4.3 TELEHEATLH 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 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.

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.

4.4 PARTICIPANT REGISTRATION

Research participants who sign an informed consent document for any Center for Cancer Research (CCR) protocol, including multi-site studies, 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.

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

4.5 APPROVAL FOR OUTSIDE MEDICAL SERVICES

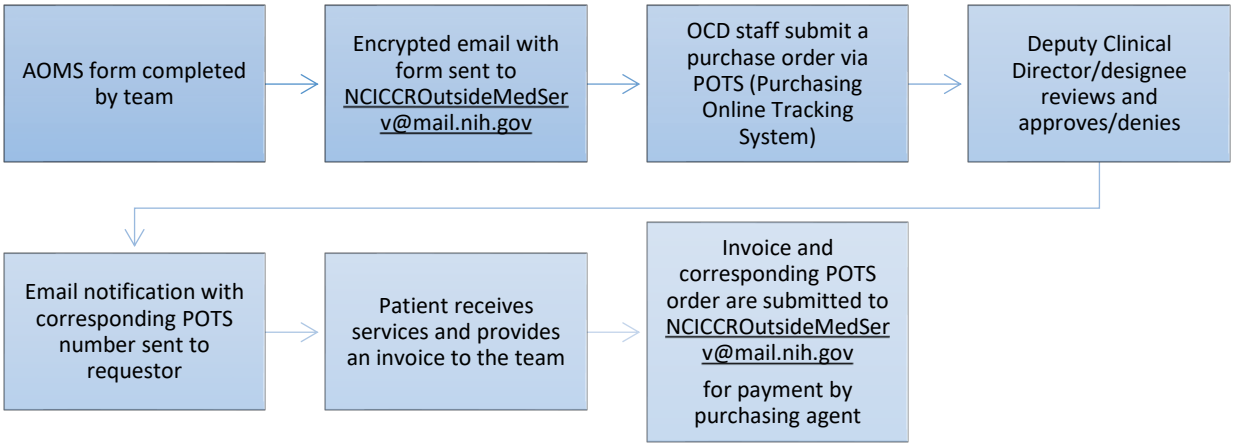
If research procedures/required medical services cannot be conducted at the NIH Clinical Center and are available at an outside facility, these research procedures/medical services may be paid by the NCI Center for Cancer Research. Approval of payment must be secured ***prior*** to the services being rendered to the participant. You should never obligate/promise funds on behalf of the government without an approved purchase order. We 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 called an Authorization for Payment for Medical Services Outside the Clinical Center form (NIH CC Form 2541). 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, Cheryl Royce (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 you still need to plan ahead.

Below is a depiction of the Process for submission of an AOMS request:



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.
        - 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.

4.6 COLLABORATING WITH OUTSIDE FACILITIES

There are situations when patients may need to be transferred to an outside facility because the medical services required for them are not available at the Clinical Center.

4.6.1 WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC)

The CCR and WRNMMC have developed numerous collaborations, fostered by close proximity and mutually beneficial clinical and research partnerships. The following information serves to assist CCR investigators in developing collaborations with WRNMMC. Collaborations have been developed to allow for the temporary transfer of NCI CCR patients from the NIH Clinical Center to WRNMMC to provide clinical expertise and services not currently available at the NIH.

First step is to contact the Deputy Clinical Director, Cheryl Royce, or the Acting Clinical Director, Dr. James Gulley. The approval for patient transfer is given on a case-by-case basis. The following link provides a description of the process and the steps necessary for approval, transfer, and treatment. We do not have the capability for emergency or weekend transfers. This process takes up to two weeks to complete. The process is outlined on the CCR Clinical Research Operations page found at:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Collaborating+with+Walter+Reed+National+Military+Medical+Center+%28WRNMMC%29+Murtha+Cancer+Center

Our current contact at WRNMMC is Denise M. Wright. When we utilize WRNMCC versus other supportive sections at WRNMMC are as follows:

- Murtha Cancer Center (MCC) Secretarial Designee (SECDES) program is for patients with a known or suspected cancer diagnosis to receive services at WRNMMC for the purpose of treatment at the Murtha Cancer Center.
- WRNMMC External Partnership Referral Office (EPRO) can assist with transferring NIH patients for non-oncology related appointments/procedures.

If the patient does not meet the criteria for MCC SECDES, please contact the WRNMMC EPRO office for assistance:

Claudia Ramirez
External Partnership Referral Office (EPRO)
Walter Reed National Military Medical Center
301-400-0404 Office
202-491-5665 Cell
Claudia.m.ramirez9.civ@mail.mil
dha.bethesda.ha-support.list.wrnm-epro@mail.mil

or

Michelle Boddie
Health System Specialist
External Partnership Referral Office

Walter Reed National Military Medical Center Bldg. 9 1st Floor, Rm 1323B
8901 Wisconsin Avenue
Bethesda, Maryland 20889-5600
Work: 301-319-4632
W(cell) – 202-491-3682
Fax: 301-319-8555
Email: michelle.d.boddie.civ@mail.mil

4.7 REQUIRED ACTIVITY FOR NEW CRC HIRE

1. Read CCR SOP ADCR-2 *CCR Participant Registration & Status Update*
2. View the PRES training video
3. Read CCR SOP ADCR-14 *Authorization of Outside Medical Services (AOMS) for Research Participants*
4. Review ThinkAndor® resources and M2P2 #71

4.8 ADDITIONAL RESOURCES

- PRES User Guide
- PRES Login

5 OVERVIEW OF CLINICAL RESEARCH

5.1 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.

5.2 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	Assessment of risks and benefits by investigator and IRB

• Human participants should not be harmed. • Research should maximize possible benefits and minimize possible risks.	
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.

5.3 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.

5.4 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.

5.5 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.

5.5.1 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 Team Lead to see if you should report the suspected misconduct.

5.6 REQUIRED ACTIVITY FOR NEW CRC HIRE

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

5.7 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

6 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.

6.1 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.

6.1.1 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.
Your PSO Manager will work with the PI 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.

6.1.2 SECONDARY RESEARCH

As a CRC, your PI or another investigator on your team may ask you about using biospecimens to study another research question so it's important that you understand what this means so you can better advise the investigator. 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 researcher, remember that a tech transfer agreement will be needed. See Section 6.2.2 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.

6.2 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.

6.2.1 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 to you by your 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), using the DEC Submission form in iRIS. This will be done by your PSO manager. Once the IC DEC has completed the review of the protocol, the COI outcome letter is uploaded in iRIS by your PSO manager assuring the IRB that NIH COI requirements have been met.

As a CRC, you are required to complete one of two forms:

- For federal employees, you will need to 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 you instructions.

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

6.2.2 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 <u>but not provide funds directly to CRADA collaborator</u> • 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

6.2.3 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 amendments 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 listserve (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.

6.2.4 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. User guides can be found at:
https://irbo.nih.gov/confluence/display/ohsrp/NIH+PROTECT+Training+and+User+Guides.

During the development of the protocol, your PSO manager will work with the PI 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, as a CRC, you should be aware of when RSC approval is required and when RSC review is approved.

6.2.5 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. Your PSO Manager will work with the PI to ensure that applicable protocols are submitted in the relevant electronic review system and be reviewed by the NIH IBC.

6.3 DATA MANAGEMENT AND SHARING (DMS) PLAN

Under development

6.4 REQUIRED ACTIVITY FOR NEW CRC HIRE

1. Federal CRC: Complete the HHS Form 717-1 form once contacted by the NCI Ethics Office for federal employees and for contractors
2. Contract CRC: 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. 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.

6.5 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

7 INSTITUTIONAL REVIEW BOARD

7.1 ELECTRONIC IRB MANAGEMENT SYSTEM: PROTECT

PROTECT is the Huron IRB electronic submission system used by the NIH IRP IRB.

7.2 INITIAL REVIEW

7.2.1 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.

7.2.2 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.

7.2.3 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.

7.3 REQUIRED ACTIVITY FOR NEW CRC HIRE

7.4 ADDITIONAL RESOURCES

- NIH Investigator Manual for Human Subjects Research

8 POST INITIAL IRB APPROVAL

8.1 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.

The CCR's 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.

8.2 MODIFICATIONS

Under development

8.2.1 AMENDMENT/MODIFICATION TRAINING

The PI is responsible for ensuring that all study staff are updated when a protocol amendment 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.

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

8.3 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.

8.3.1 INFORMATION TO BE SUBMITTED IN THE CR

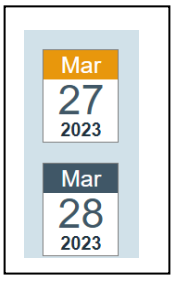
The continuing review submission consists of a form in PROTECT on which the researcher records any changes, incidents or other problems that have occurred since the study was approved, or since the previous continuing review. Your PSO Manager will send you and the PI a word document to be completed that contains all the information needed for the CR form in PROTECT.

8.3.1.1 REDACTED COPY INFORMED CONSENT (IC) DOCUMENT(S)

The last IC document of each version of the study's consent, including assent that has been used since last CR need to be uploaded into PROTECT. If informed consent was not obtained during the CR period, please note this in the CR summary. The CRC is responsible for redacting the patient information (name, MR# and date of birth) from each page of the IC document(s). Make sure to redact printed patient name and signature - do not redact investigator signature or **any** signature dates. For instructions on how to redact IC document, visit the Adobe website at: https://helpx.adobe.com/acrobat/using/removing-sensitive-content-pdfs.html.

8.3.2 CR NOTIFICATION PROCESS

You will receive CR reminders from PROTECT. Your dashboard will also show all your 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 study team and PSO manager about upcoming continuing review deadlines. Your PSO manager will send you an email with the questions, the data cut-off date, and a due date for the study team (ahead of the IRB deadline) to return the requested information.

You will work with your PI to answer the requested questions and 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.

You will receive an NIH IB Approval memo from PROTECT via email once your CR has been reviewed with your approval status and stipulations to address, if applicable.

8.3.3 TIPS

Reference your last continuing review and update the answers to maintain consistency. You can find approved CRs in PROTECT and the protocol's regulatory file. Keep your PDTS data entry and SAE logs up to date in real time. Prioritize verifying adverse events in the clinical database (e.g., C3D, RAVE, LabMatrix) as these are needed for multiple regulatory reports. You and the PI may want to create a table of results that are updated periodically to help answer the question about progress/findings for treatment studies.

Note: For some studies, a progress report may be required (i.e., data analysis only) – these are for minimal risk studies and contain fewer questions. The questions are subject to change over time per the IRB. You will have a couple of weeks to return your answers to the PSO.

8.4 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 you and the PI with the required content a few weeks in advance of the due date. Please note that the same IND may be used for multiple protocols across different teams and branches. You and your PI are only responsible for the content for your own protocols. The OSRO IND team will compile the rest.

So, what do you need to do as a CRC? Verify adverse events in the CCR database up to the cut-off date, then ask your data manager to pull the relevant AE table from j-review, if applicable. You will need to include the table in your response, and it will also help you summarize the toxicities. Run a report in PRES to confirm all the demographic questions – see PRES Manual for the report. Work with your PI to answer the rest of the questions about off study reasons, results, investigational plan for the upcoming year, manufacturing changes, publications, etc. It is helpful if you reference the last FDA Annual Report to maintain consistency. If you have a cell therapy protocol that requires long term follow up from the FDA, you 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. Your job is to make sure the data in the database is complete. You can expect to receive more database queries leading up to the FDA Annual Report due date that you will need to address.

8.5 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.

8.5.1 STEPS TO CLOSE A STUDY

Under development

8.6 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.

8.6.1 REPORTING THE PRIMARY COMPLETION DATE

The Responsible Party (i.e., the PI) must report the primary completion date to the Office of Protocol Services (OPS) 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.

8.6.2 PI NOTIFICATION

Our Program Analyst 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 CC Office of Protocol Services (OPS), Kim Mitchell, 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

8.6.3 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 Analysist 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.

8.6.4 COMPLIANCE

PIs must be compliant per the NIH Manual Chapter 3007 – Clinical Trial Registration and Results Reporting Information. The CC OPS 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 OPS.

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 complaint or leadership will start implementing other consequences for non-compliance after 30 days.

8.7 REQUIRED ACTIVITY FOR NEW CRC HIRE

1. Read SOP PM-5, *Research Protocol Training Requirements*
2. Read SOP PM-9, *Research Team Amendment Training*
3. Review M2P2 #17 *What information needs to be reported to the IRB at the time of continuing review (CR)?*
4. Review M2P2 #41 *What is the primary completion date (PCD) and the anticipated completion date (ACD)? Why are these dates important?*

8.8 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
- Adobe User Guide - Redacting Consents.pdf
- 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*

9 OVERVIEW OF ROLES & RESPONSIBILITIES

To learn more about key roles and responsibilities of the research team, please refer to the *Responsibilities of the Research Team* online learning module.

9.1 INVESTIGATOR

An Investigator is an individual who is involved in the conduct of human subjects research. Such involvement 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, 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*

9.1.1 PI DELEGATION OF RESEARCH TASKS

It is common for the PI to delegate certain study-related tasks 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 Tasks (DOT) log for the PI and the monitor will review the log at each monitoring visit.

In the CCR, all research studies (interventional and observational) are required to have a DOT 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.

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

- CCR SOP PM-1 *Delegation of Tasks for Research*
- Guidelines for Completing the Delegation of Tasks Log
- Delegation of Task Log

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.

9.2 CLINICAL RESEARCH COORDINATOR

Under development

9.3 DATA MANAGER

Under development

9.4 NURSE PRACTITIONER/PHYSICIAN ASSISTANT

Under development

9.5 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
- Requests, retrieves, and delivers samples and information from external providers related to research patients, needed for study teams
- 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

9.6 CLINICAL CENTER NURSING

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.

9.6.1 WORKING WITH THE DAY HOSPITAL (3SES)

The day hospital (DH) provides care for adult patients with hematologic disorders and malignancies, solid tumor cancers and immunodeficiencies enrolled in a variety of National Institutes of Health (NIH) research studies. For new CRCs Legna Hernandez provides a 2-hour orientation to the DH which includes a tour and how to effectively work with the DH. Contact her via email to set up an appointment.

The oncology and critical care service protocol impact query (PIQ) system facilitates the scheduling of patients who need treatment, blood draws and/or supportive care. You will need to complete the PIQ form to provide a concise synopsis of the new protocol. This form is also used by respective units/clinics to evaluate the intensity of the protocol's impact. This is an essential step in protocol implementation. At least four (4) weeks prior to protocol implementation in the DH, you will need to do the following:

- Complete the PIQ Form (see Appendix C) and send it via email to CC-NURS OCC Protocol Impact Query Team with the subject line "PIQ Form." You will receive an acknowledgement notice within 72 hours.
- Once this information is obtained, the DH protocol coordinator or designee in collaboration with Unit/Clinic leadership will review the protocol and collaborate with you to make the necessary adjustments to support protocol implementation. These adjustments may include:
    - Making special arrangements with different departments (EKG-imaging or molecular diagnostic test)

- Obtaining special tubes for PK's or PD (laboratory tests)
- Developing patient education materials
- Altering staffing patterns to support day and timing of treatments (anticipate adequate staffing)
- Anticipating unit-based staff education (including disease, new equipment, medication, side effects, new high risk nursing skill and competencies)

- The DH protocol coordinator or designee will contact the research team to coordinate an in-service. It is recommended that in-services be scheduled within two weeks preceding the first patient arrival. If applicable. PK/PD worksheets need to be available for the in-service.

9.6.2 WORKING WITH 3NW

The 3NW unit is an adult inpatient unit supporting the research of the National Cancer Institute (NCI), National Institute of Dental and Craniofacial Research (NIDCR) and National Heart, Lung and Blood Institute (NHLBI) along with institutes requiring surgical consults for solid tumor cancers, pre and post-operative care, new and unstable tracheostomy management, telemetry care/monitoring and wound and skin care consultation service by certified Wound Care Nurses (WOCN).

For patient admissions to 3NW, complete the 3NW Admission Request Form and email to the CC-NURS 3NW Admissions. Please make sure all requests are emailed two weeks prior to the anticipated admission date.

9.7 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.

9.8 PHARMACY

Under development

9.9 SPONSOR

Under development

9.10 REQUIRED ACTIVITY FOR NEW CRC HIRE

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 *Delegation of Tasks for Research*
5. Read Guidelines for Completing the Delegation of Tasks Log
6. Review the Delegation of Task Log
7. Contact Legna Hernandez to schedule orientation to the day hospital.

9.11 ADDITIONAL RESOURCES

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

10 PATIENT RECRUITMENT AND REFERRALS

10.1 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.

10.2 GENERAL PRINCIPLES REGARDING REFERRALS

Regardless of whether your team utilizes one of the referral offices, there are general principles regarding referrals. You may 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 you are representing NCI and NIH. Many patients or family members have anxiety placing these calls or emails and do not know how the system works. If you receive a phone call or email regarding a referral, reply within 24-hours.

As a CRC, you will need to understand how your research team manages referrals. If there is a specific person on your 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 your research team's decision to accept or not accept international referrals. If your team does accept international patients,

are there certain caveats per protocol? For example, patients must speak English, or patients must stay in the area for X weeks. If you receive a foreign language phone call, you can return the call utilizing the CyraCom language line. See Appendix D for instructions.

Pre-screening referrals begins with this phone call or email. Basic information is needed including the diagnosis, therapies received (if any), performance status (PS), and location of patient (e.g., in U.S.? what state?). 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 your team's studies are designed for patients who have had at least one regimen of standard care. The caller explains he or she was diagnosed with cancer last week and wants to get into your 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 study
- 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
- Demographics to contact 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 patient seems like a good candidate based on the record review, the radiology images are then reviewed by the CCR 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 pathology or HLA typing is required for eligibility, patients must be registered on a screening protocol prior to submitting material to pathology. This may require a phone consent and ex loc registration. There are processes in place for both and your protocol should allow for this. See SOP ADCR-13 *Clinical Center External Location Registration* 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.

10.3 THE MEDICAL ONOCLOGY REFERRAL OFFICE (MORO)

The MORO is the referral point of contact for many study teams within the CCR. Check with your team to see if you are using MORO for your referrals. MORO 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 study team.

Records received will be bookmarked in Adobe and placed in the CCR Referral Application: https://ccrreferrals.nci.nih.gov/. If you 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 foreign countries. That is the research team's responsibility.

MORO works with the following teams:

- Pediatric Oncology Branch (POB) Solid Tumor, NF1, and Rare Tumor
- Genitourinary Malignancy Branch (GMB)
- Thoracic Medical Oncology
- GI Medical Oncology
- Developmental Therapeutics Branch
- Urological Oncology Branch (UOB) Kidney/Kidney Therapeutics
- Women's Malignancy Branch (WMB)
- Lymphoma
- Myeloma
- Metabolism
- Molecular Imaging Branch

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

10.4 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 our 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 the 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 updates/amendments 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.

10.5 REQUIRED ACTIVITES FOR THE NEW CRC HIRE

Below is a list of activities to be completed to help you learn more about the referral process:

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. Review the studies currently open and recruiting in your team. What are the diagnoses required for eligibility? Is there a requirement for prior therapy?
4. Listen to at least 2 phone calls between your team member/preceptor/referral nurse and referring individual; both those who are potentially eligible and those who are not
5. Review at least 2 emails from your team to MORO regarding a referral if your team utilizes the services of MORO
6. Review the *CCR Referrals Application Training Guide* if your team utilizes the services of MORO
7. Review the process of uploading images to the NIH Radiology drop box and bookmark this page: https://cc.nih.gov/dcri/imaginglibrary.html
8. Review the process of submitting pathology materials once a patient is appropriately consented and registered (*to be developed*)
9. Review M2P2 #54 *What should I do to get biologic material (e.g., pathology samples) from outside the U.S. to the NIH?*

10. Review the process of using the Cyracom language line. See Appendix D.

10.6 ADDITIONAL RESOURCES

11 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, for us 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 and adults who are unable to make their own decisions regarding research participation, a legally authorized representative (LAR) is needed. You may not enroll or involve a subject in any research activities, until legally effective informed consent has been obtained.

Both the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) regulations address informed consent that you need to familiarize yourself with:

- 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/IRB application 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
- CCR SOP PM-2 *Obtaining and Documenting the Informed Consent Process (Adult and Pediatric)*
- 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

11.1 INFORMED CONSENT DOCUMENT (ICD)

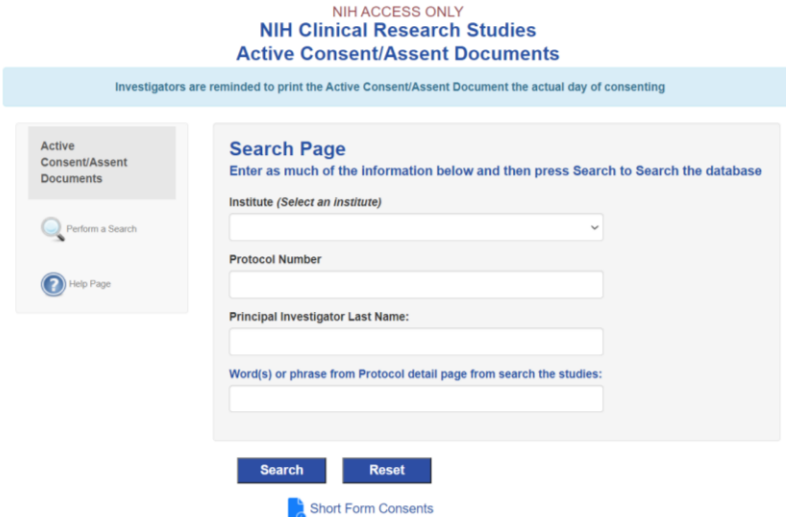
The informed consent document (ICD) is the IRB-approved written record that is compliant with the regulations and is used to demonstrate the consent by a subject/LAR to participate in research. It explains what will be done and the subjects' rights. It should be written in a language understandable to the subject and contain no exculpatory language. Your PSO Manager will develop the ICD, but as a CRC, you should be reading the ICD as well since that is what your patient 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. See *User Guide MEDConsent™*.

11.2 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 with assigned task of informed consent; and
- Listed on the delegation of task 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.

11.2.1 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 you or the PI 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 you can 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

11.3 INFORMED CONSENT PROCESS

Below is a schematic of the informed consent process.

Step 1
- A copy of the ICD is given to the potential subject (i.e., individual). Investigator verbally explains the study to the individual providing all required information. The potential subject is then given enough opportunity to ask questions.

Step 2
- The individual is given sufficient time to discuss with family, friends, and other physicians. Sufficient time means hours to days depending on the type of study.

Step 3
- After allowing the individual time to read the ICD, an investigator should meet with the individual and answer any additional questions.

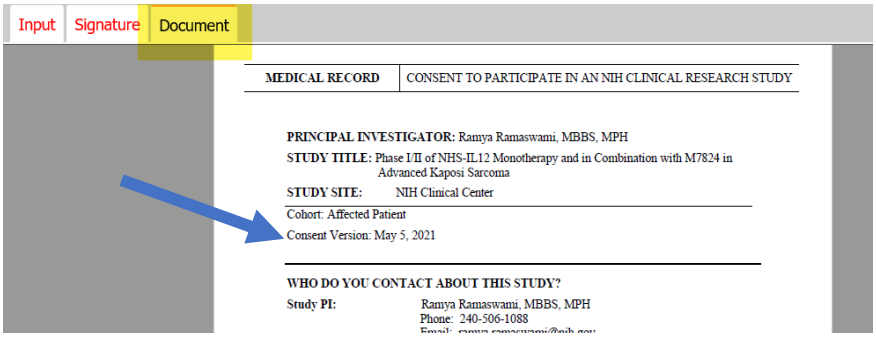
Step 4
- After all questions are answered and the individual agrees to participate, the individual initials the embbedded questions, if applicable, then signs and dates the IC document. The consenting investigator signs the consent. Other signature(s) may be required for non-English speaking subjects.

Step 5
- A copy of the signed ICD is given to the individual and the original goes in the individual 's medical record.

Step 6
- Investigator who obtains the consent will document the process in CRIS. However, if another team member was also part of the discussion, they can write the note on behalf of the consenting investigator.

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"

11.4 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).

11.5 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 MS Teams, can be used when conducting a consent via video. 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 *Obtaining and Documenting the Informed Consent Process (Adult and Pediatric):*

- Send current IRB approved ICD to patient and set up time to discuss
- Confirm ID of patient
- Review entire ICD
- Ask patient if he/she agrees 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 risk the date of their signature being different than the date of the conversation which becomes a minor deviation.
- 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.
- 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*

11.6 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.

11.7 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.

11.8 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:

- You anticipate this to happen based on the study population
- You don't anticipate this to happen. This is also referred to as the short form consent process

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 translator 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 Translator*
- 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?*

11.8.1 TRANSLATOR/INTERPRETER SERVICES

Whenever possible, a professional interpreter, who is in-person, should be used or, alternatively, professional translation can be via a phone translation service. Use of a family member for interpretation is not permitted unless a professional medical translator cannot be located. The reasons for using a family member and the attempts made to locate a professional translator 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, you must document in CRIS the reasons for using a family member and the attempts made to locate a professional translator.

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 if the language needed is not a common language (e.g., Mandarin), more than 24 hours may be needed to secure an interpreter.

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

11.8.2 TRANSLATION SERVICES

There are times when you will need to have either the English long form IRB approved ICD or the English short form ICD translated into another language.

The NIH Library Translation Services provides written translations of materials including ICDs and certificates of accuracy. There may be a fee associated with the translation of an ICD. Visit the NIH Library Translation Services website to learn more including those languages that are free of charge. The website also provides an online request submission form. Your PSO Manager will facilitate this process, but they must know as soon as possible. Depending on the language requested and the length of the consent, this may take days to weeks.

11.8.3 ANTICIPATED ENROLLMENT

When non-English speaking subjects are anticipated to enroll in a particular research protocol, 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.

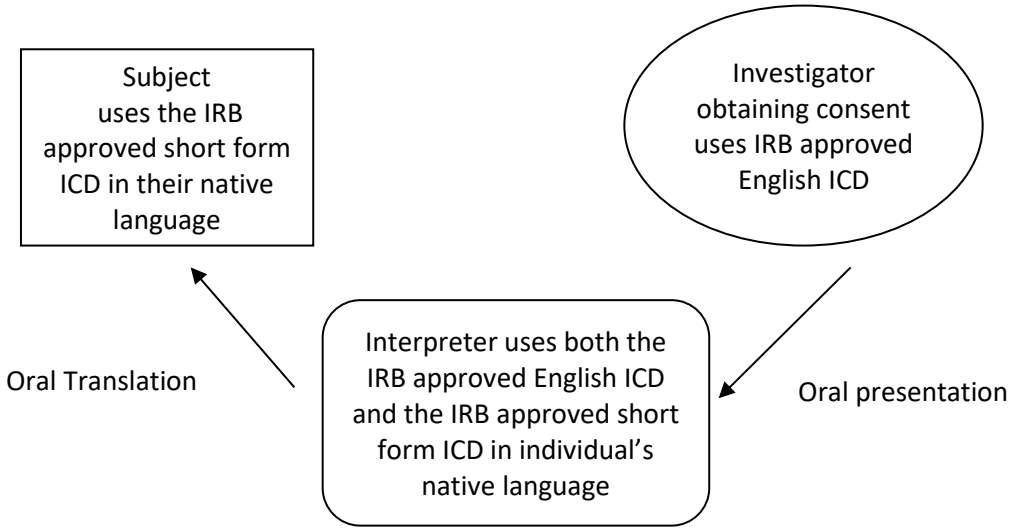
11.8.4 UNEXPECTED ENROLLMENT – SHORT FORM PROCESS

When a non-English speaking subject seeks to enroll unexpectedly 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, or
- If there is no IRB-approved short form consent document in the language of the subject, the PI must submit to the IRB a certified translation of the short form consent in the language for approval by the IRB before the patient can be consented.

Until there is a translated short form, the patient may not be enrolled. Work with your PSO manager and the NIH Library Translation Services (see section 11.8.2) to secure the short form. Once you receive the translation, submit the translated short form and the certificate of accuracy to the IRB via iRIS using an amendment form.

Below is a schematic of what the 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.

11.9 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.

11.10 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
    -

11.11 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 SOP also states 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 4 tabs: protocol ID, consent type, consent process and comments. After selecting the protocol ID, you will need to select ALL the consent types used during the informed consent process:

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

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. You must answer "Yes" or "No." If you answer "No" a text box will appear that requires an explanation. For example, if you are doing a remote consent, you will not be able to answer "Yes" to the statement "A Copy Of The Consent, Signed And Dated By The Investigator And Participant Was Given To The Participant." You would answer "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 you would 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.

11.12 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 you 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?*

11.13 REQUIRED ACTIVITIES FOR NEW CRC HIRE

1. *Compete the Informed Consent* online learning module
2. Read HRPP Policy *301 Informed Consent*
3. Read HRPP Informed Consent FAQs
4. Read CCR SOP PM-2 *Obtaining and Documenting the Informed Consent Process (Adult and Pediatric)*
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?*

11.14 ADDITIONAL RESOURCES

- OHRP Informed Consent FAQs
- OHRP Informed Consent videos

12 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

The CRC is responsible for ensuring that necessary source documents are present and maintained in an organized manner - they provide the "story" of the clinical trial and this validates compliance with the protocol and integrity of the study data.

12.1 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*

12.2 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

See the HIMD organizational chart.

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.

12.3 RESEARCH RECORD

Under development

12.4 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 your role in ensuring this.

12.4.1 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. If you have a protocol 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.

12.4.1.1 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 check-In in front of the Patient Travel Office (1-4553) near the atrium with a pharmacy rep. When the medication is ready, they pick it up at 1N259. Self-administered medications are documented by the patient on a diary (found in the appendix of your protocol usually). 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. You are required to use it without altering it.

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, you should have the next diary ready for the patient with the dose prescribed notated and the dates already entered for them.

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.*

12.4.1.2 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. You should follow up with the patient to ensure they received the medication(s) and that there was nothing damaged.

If your 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*.

12.5 REQUIRED ACTIVITY FOR NEW CRC HIRE

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*

12.6 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

13 ESSENTIAL DOCUMENTS

Under development

13.1 REQUIRED ACTIVITIES FOR NEW CRC HIRE

13.2 ADDITIONAL RESOURCES

14 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. Your protocol may also contain these important definitions. See Appendix E 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).

14.1 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. As a CRC, you may need to remind the provider to do this. 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 E 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. As a CRC, you are well positioned to assist with AE assessment which is particularly true for nurse CRCs.

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?

14.2 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 with version 6.0 anticipated to be published in the Fall of 2022. Current and recent past versions of the CTCAE

can be found on CTEP's website. You can also download CTCAE app to your phone or tablet which then offers search features.

14.2.1 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.

14.3 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 (Ped-PRO-CTCAE®). 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 (Ped-PRO-CTCAE®[Caregiver]). The pediatric module includes 130 items representing 62 symptomatic events drawn from the CTCAE.

14.4 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.

14.5 REQUIRED ACTIVITIES FOR NEW CRC HIRE

1. Complete Parts 1 and 2 of the *Adverse Event* online learning module

14.6 ADDITIONAL RESOURCES

15 EXPEDITED REPORTING OF ADVERSE EVENTS AND OTHER EVENTS

15.1 EXPEDITED REPORTING OF AES FOR IND/IDE TRIALS

As a CRC, you will 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, you are the one delegated to submit these AEs. 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. Remember, you can reach out to one of your colleagues, your team lead, or staff from the Office of Education and Compliance who can help you discern what needs to be reported and how to report it.

15.1.1 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. 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 as a CRC, you will need to know how your sponsor is to receive an SAE and to familiarize yourself 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 your data manager. They will need to make sure the same data is collected on the routine AE CRF. Second, send the final report to your 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.

15.1.2 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.

15.2 IND SAFETY REPORTS

Under development

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

Under development

15.4 REPORTING TO THE CLINICAL DIRECTOR

Under development

15.5 REQUIRED ACTIVITIES FOR NEW CRC HIRE

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

15.6 ADDITIONAL RESOURCES

16 CLINICAL DATA MANAGEMENT

Under development

16.1 REQUIRED ACTIVITIES FOR NEW CRC HIRE

16.2 ADDITIONAL RESOURCES

17 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.

17.1 TYPES OF MONITORING VISITS

17.1.1 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.

17.1.2 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.

17.1.3 INTERIM MONITORING/ROUTINE MONITORING VISIT (IMV/RMV)

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.

17.1.4 CLOSEOUT VISIT

Under development

17.2 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.

17.3 PREPARING FOR A VISIT

Under development

17.4 REQUIRED ACTIVITIES FOR NEW CRC HIRE

1. Complete Part 1 of the *Monitoring and Auditing in Clinical Trials* online learning module
2. Review the HIMD Regulatory Audit Guide
3. Read CCR SOP PM-13 *Industry-Sponsored Studies Monitoring and Audit Visits*
4. Read CCR SOP PM-13a *Center for Cancer Research Sponsored Studies Monitoring and Audit Visits*
5. Read CCR SOP PM-13b *Monitoring and Audit Visits by ASRC (Artic Slope Regional Corporation)*

17.5 ADDITIONAL RESOURCES

18 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, to presentations, publications, and membership in professional nursing and 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 to enhance your professional development. As part of PD in the CCR, the Office of Education and Compliance provides webinars and there are other activities throughout the NIH IRP that are available to you as well. For nurse CRCs, nursing professional development contact hours are awarded.

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

Core to supporting your competence as a CRC, 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.

18.1.1 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 as a CRC. 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 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.

18.1.2 PROFESSIONAL DEVELOPMENT LOG

Another important aspect of your professional development is maintaining your Professional Development Log. This log should be downloaded and saved to your personal drive and kept in a folder that can be easily accessed in order to update the log in real time. It includes tracking your continuing nursing education, continuing medical education, academic education, publications, presentations, precepting, and volunteer leadership services as you complete them throughout the year. Reviewing your PD log at the time of your PMAP, can help you identify your learning needs and what learning activities you've already achieved. Below are the professional development activities offered in the CCR and the NIH IRP. You will learn about these activities via email because you are on the CCR ORN distribution list and other CCR/IRB lists.

18.2 PROFESSIONAL DEVELOPMENT ACTIVITIES

The complex and rapidly growing 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 the recommended continuing education for CRCs. 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.

18.2.1 ONCOLOGY BROWN BAG LUNCHES (BBL)

The Oncology Nursing Brown Bag Lunches 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 BBL 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 Nursing Brown Bag Lunch schedule along with past presentations is located on the Education and Training page. Nursing professional development contact hours are awarded.

18.2.2 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. They are held monthly. The CCR Clinical Research Forum schedule along with past presentations is located on the Education and Training page. Nursing professional development contact hours are awarded.

18.2.3 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 professional development contact hours are awarded.

18.2.4 OTHER ACTIVITIES

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

18.2.4.1 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.

18.2.4.2 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.

18.3 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 nursing 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 evaluation, 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.

18.4 PROFESSIONAL ORGANIZATIONS

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

18.4.1 FOR CRCS

18.4.1.1 ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS (ACRP)

The Association of Clinical Research Professionals (ACRP) was founded in 1976 and supports clinical research professionals. 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.

18.4.1.2 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. 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.

18.4.2 FOR NURSE CRCS

18.4.2.1 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.

18.4.2.2 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 annual conference is held in October.

18.5 CERTIFICATION

Certification is formal recognition based on specific criteria with established parameters that reflect assessment of educational preparation and knowledge, skills, and abilities or competence developed through experience in a specialty area of practice. Certification promotes public safety by establishing minimal competency standards for CRCs who have met those standards.

18.5.1 CRC CERTIFICATIONS

Both ACRP and SoCRA offer research specific certification. ACRP offers 4 types of certifications based on your role. For you as a CRC, the clinical research coordinator (CCRC®) certification is the best fit. SoCRA offers one certification program, the certified clinical research professional (CCRP®).

18.5.2 NURSE CRC CERTIFICATIONS

18.5.2.1 ONCOLOGY NURSING CERTIFICATION CORPORATION (ONCC)

The Oncology Nursing Certification Corporation (ONCC) is the premier provider of nationally accredited certification for nurses in oncology and related specialties. It was founded in 1984 and administered the first Oncology Certified Nurse (OCN®) examination in 1986. Through ONCC, there are over 40,000 certified nurses. Currently, ONCC offers eight certification programs:

- Oncology Certified Nurse (OCN®)
- Certified Pediatric Hematology Oncology Nurse (CPHON®)
- Certified Breast Care Nurse (CBCN®)
- Blood & Marrow Transplant Certified Nurse (BMTCN®)
- Advanced Oncology Certified Nurse Practitioner (AOCNP®)
- Advanced Oncology Certified Clinical Nurse Specialist (AOCNS®) (renewal only)
- Certified Pediatric Oncology Nurse (CPON®) (renewal only)
- Advanced Oncology Certified Nurse (AOCN®) (renewal only)

18.5.2.2 CLINICAL RESEARCH NURSING CERTIFICATION COUNCIL

The Clinical Research Nursing Certification Council (CRNCC) is the only organization that formally recognizes the specialized body of knowledge unique to the clinical research nurse. Established in 2020, the purpose of CRNCC is to establish and maintain excellence in the specialty practice of clinical research nursing through credentialing (CRN-BC™). The CRN-BC™ directly or indirectly impacts the care of clinical research participants across the care continuum in all clinical specialties and settings, ensuring protection of consumers engaged in clinical research and the public who benefit from research discovery. Certification is through portfolio. Visit their website to learn more.

18.6 REQUIRED ACTIVITIES FOR THE NEW CRC HIRE

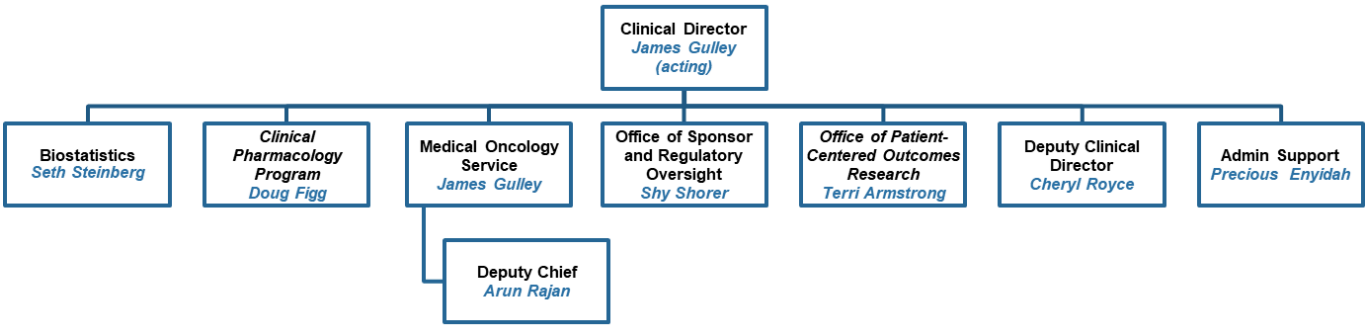
1. Develop or revise existing CV to include current research nurse role

18.7 ADDITIONAL RESOURCES

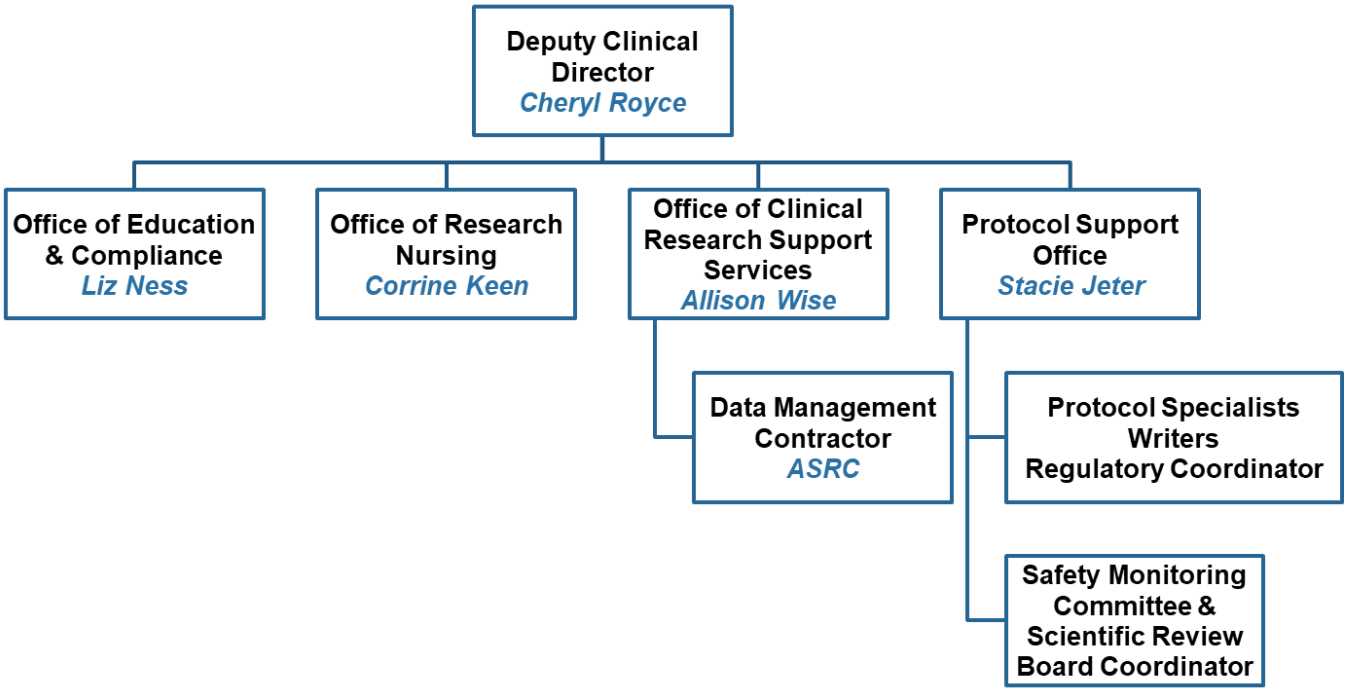
- CCR Education and Training website

19 APPENDICES

19.1 APPENDIX A: OFFICE OF THE CLINICAL DIRECTOR ORGANIZATIONAL CHART



APPENDIX B: OFFICE OF THE DEPUTY CLINICAL DIRECTOR ORGANIZATIONAL CHART



19.2 APPENDIX C: DAY HOSPITAL PROTOCOL IMPACT QUERY

Oncology and Critical Care Service

Protocol Impact Query Form

<table>
<tr><td>Protocol Title</td><td colspan="3"></td></tr>
<tr><td>Protocol Number</td><td colspan="3"></td></tr>
<tr><td>Research Type</td><td colspan="3">☐ Observational ☐ Interventional</td></tr>
<tr><td>Principal Investigator</td><td colspan="3"></td></tr>
<tr><td>Associate Investigator(s)</td><td colspan="3"></td></tr>
<tr><td>Research Nurse Coordinator & Phone number</td><td colspan="3"></td></tr>
<tr><td>Patient Population (disease, newly diagnosed, relapsed, etc.)</td><td colspan="3"></td></tr>
<tr><td>Anticipated Visit Location(s)
(Check all that apply)</td><td colspan="3">INPATIENT UNIT: Choose an item. Other: _____
ICU ☐
OUTPATIENT CLINIC: Choose an item.
3 SE DAY HOSPITAL: ☐</td></tr>
<tr><td>Number of Patients to be enrolled</td><td colspan="3"></td></tr>
<tr><td>Anticipated first treatment</td><td colspan="3"></td></tr>
<tr><td rowspan="6">Treatment Schema</td><td colspan="3">Study Drugs:</td></tr>
<tr><td colspan="3">Anticipated Length of infusion(s):</td></tr>
<tr><td colspan="3">Total length of treatment:
(Including pre-meds, pre-hydration, etc.)</td></tr>
<tr><td colspan="3">Length of the cycle:</td></tr>
<tr><td colspan="3">Treatment Day(s) of the Week:</td></tr>
<tr><td>INPATIENT UNIT
Anticipated Length of Stay: ____</td><td>3 SE DAY HOSPITAL
Anticipated Duration of Visit(hrs): ____</td><td>OUTPATIENT CLINIC
Clinic/Visit Day of week</td></tr>
</table>

	Cycle/Day/Frequency:	Cycle/Day/Frequency:	Choose an item. Cycle/Day/Frequency:
Anticipated Side Effects			
Protocol Requirements Pre, During and Post Study Drug Administration	Observation Time: Vital Signs frequency: Telemetry Monitoring: ☐ Yes ☐ No Additional diagnostic test (EKG/X-Ray/Saliva/Biopsy etc.):		
Access device required by protocol	☐ Central VAD ☐ Peripheral VAD ☐ Other: _____		
Special Equipment required by protocol *(i.e. syringe pump, etc.)*			
INPATIENT UNIT **Pharmacokinetics (PK) / Pharmacodynamics (PD)/ Research blood** ***(Attach PK Sheet if applicable)***	☐ Not Applicable (N/A) ☐ See Section ___ of protocol for research lab details Can PK/PD be drawn from the same lumen as drug infusion? ☐ Yes ☐ No Can PK/PD be drawn from the same site/arm as drug infusion? ☐ Yes ☐ No Cycle/Day/Frequency: *Special Instruction(s):*		
3 SE DAY HOSPITAL **Pharmacokinetics (PK) / Pharmacodynamics (PD)/ Research blood** ***(Attach PK Sheet if applicable)***	☐ Not Applicable (N/A) ☐ See Section ___ of protocol for research lab details Can PK/PD be drawn from the same lumen as drug infusion? ☐ Yes ☐ No Can PK/PD be drawn from the same site/arm as drug infusion? ☐ Yes ☐ No Cycle/Day/Frequency: *Special Instruction(s):*		
OUTPATIENT CLINIC **Pharmacokinetics (PK) / Pharmacodynamics (PD)/ Research blood** ***(Attach PK Sheet if applicable)***	☐ Not Applicable (N/A) ☐ See Section ___ of protocol for research lab details Can PK/PD be drawn from the same lumen as drug infusion? ☐ Yes ☐ No		

	Can PK/PD be drawn from the same site/arm as drug infusion? ☐ Yes ☐ No Cycle/Day/Frequency: *Special Instruction(s):*
Days of the week preferable for In-service	****Reminder: Please email completed form to "**CC-NURS OCC Protocol Impact Query Team**"*
Additional Comment(s)	

19.3 APPENDIX D: LANGUAGE INTERPRETIVE PHONE SERVICES

The language interpretive phone service is useful for the PCC 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

19.4 APPENDIX E: 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; • results in a congenital anomaly/birth defect; or	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 hospitalization may be	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.

	• 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	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 the subject(s) experiencing the adverse event and the subject's predisposing risk	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)

	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 (2022). 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