ICTR Clinical Research Manual:

A Guide to Conducting Clinical Research at UW-Madison



UW Institute for Clinical and Translational Research

UW ICTR

May 2018

Acknowledgements

I would like to acknowledge all of the members of the Clinical Research Training Task Force who contributed significantly to the development and review of this course. The task force included representatives from a variety of disciplines, departments and programs, as well as roles in clinical research.

- UW Institute for Clinical and Translational Research (ICTR)
- UW Carbone Cancer Center (UWCCC)
- Asthma, Allergy and Pulmonary Research Center
- Department of Surgery, Clinical Research Office
- Health Sciences Institutional Review Board (HSIRB) Office
- ICTR Clinical Research Unit (CRU) within the UWHC
- Office of Clinical Trials (OCT)
- Office of Research Compliance, within the Office of the Vice Chancellor for Research and Graduate Education (OVCRGE)

I would also like to extend a sincere thank you to all involved in reviewing training modules, and offering feedback, suggestions and assistance.

Tracy L. Ohrt, UW ICTR
December 2014

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Definitions

There are many terms defined in this training. These definitions were taken from several publicly available glossaries:

- NIH Glossary & Acronym List (http://grants.nih.gov/grants/glossary.htm)
- ClinicalTrials.gov Glossary (https://clinicaltrials.gov/ct2/about-studies/glossary)
- FDA Glossary (Drugs) (http://www.fda.gov/drugs/informationondrugs/ucm079436.htm)

Acronyms

AE	Adverse Event
AFCH	American Family Children's Hospital
AHC	Academic Health Center
BLA	Biologic License Application
CAP	College of American Pathologists (lab accreditation)
CDRH	Center for Devices and Radiological Health (FDA)
CFR	Code of Federal Regulations
CIRB	National Cancer Institute (NCI) Central Institutional Review Board (NCI CIRB)
CLIA	Clinical Laboratory Improvement Amendments (lab certification)
COI	Conflict of Interest
CRC	Clinical Research Coordinator
CRCO	Clinical Research Compliance Office (UWCCC)
CRF	Case Report Form
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
CTRP	Clinical Trials Reporting Program (UWCCC)
CV	Curriculum Vitae
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DOA	Delegation of Authority
DOT	Department of Transportation
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Form
ED/SBS	Education Research/Social and Behavioral Sciences IRB
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HS IRB	Health Sciences Institutional Review Board
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICTR	Institute for Clinical and Translational Research
IDE	Investigational Drug Exemption
IIT	Investigator Initiated Trials
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Authorized Representative
MARCH	Midwest Area Research Consortium for Health

MOP	Manual of Procedures
MR IRB	Minimal Risk Institutional Review Board
MRN	Medical Record Number
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NP	Nurse Practitioner
NTF	Note to File
OAR	Outside Activities Report
OCT	Office of Clinical Trials
OHRP	Office for Human Research Protections
OIP	Office of Industrial Partnerships
PA	Physician Assistant
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Approval
PMS	Post Marketing Surveillance
PRC	Pharmaceutical Research Center
PRMC	Protocol Review Monitoring Committee
QA	Quality Assurance
QC	Quality Control
RDRC	Radioactive Drug Research Committee
RN	Registered Nurse
RS	Regulatory Specialist
RSC	Research Safety Committee
RSP	Research and Sponsored Programs
SAE	Serious Adverse Event
SCRO	Stem Cell Research Oversight
SMoR	Study Monitor of Record
SMPH	School of Medicine and Public Health
SMS	Study Monitoring Service (ICTR)
SOP	Standard Operating Procedure
SRC	Scientific Review Committee
Sub-I	Sub-Investigator
UP	Unanticipated Problem
UW	University of Wisconsin
UWCCC	UW Carbone Cancer Center
UWHC	University of Wisconsin Hospital and Clinics
UWMF	University of Wisconsin Medical Foundation
WiNHR	Wisconsin Network for Health Research
WIRB	Western Institutional Review Board
VA	Veterans Administration

Introduction

The purpose of this manual is to build on human subjects protection principles and Good Clinical Practice (GCP) standards, while describing how to apply these regulations and standards to the day-to-day conduct of clinical research studies at UW-Madison.

This manual is intended to accompany and complement the UW-Madison online course, *Basics of Conducting Clinical Research at UW-Madison*, and to serve as a resource and reference for our research staff. This manual has been written both as an introduction to those who are new to clinical research at UW-Madison, and as a refresher for more experienced clinical research staff.

The content in this manual is geared toward research staff who conduct clinical research studies within the UW Health environment, however, the majority of content will be applicable to clinical research involving human subjects in all types of settings.

The National Institutes of Health (NIH) defines a **human subject** as a living individual about whom an investigator (the researcher leading the project) conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information about the individual (http://grants.nih.gov/grants/glossary.htm). Regulations governing use of human subjects in research extend to use of human organs, tissues, and body fluids from identifiable individuals and to graphic, written, or recorded information derived from such individuals. There are other terms that may be used to refer to human subjects in research in this manual, including participant, volunteer, or subject.

The NIH glossary defines **clinical research** in broad areas including:

- Patient-oriented research. Research conducted directly with human subjects or on material of human origin such as tissues, specimens, and cognitive phenomena. This research includes:
    - Mechanisms of human disease
    - Therapeutic interventions
    - Clinical trials
    - Development of new technologies.
- Epidemiological and behavioral studies.
- Outcomes research and health services research.

Also taken from the NIH glossary, a **clinical trial** is defined as a biomedical or behavioral research study of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

- The term "prospectively assigned" refers to a pre-defined process specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo or other control) of the clinical trial.

- An “intervention” is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related processes and/or endpoints. Examples include, but are not limited, to: drugs/small molecules/compounds, biologics, devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); and, treatment, prevention, and diagnostic strategies, including the use of one of the above compounds for imaging.

- A “health-related biomedical or behavioral outcome” is defined as the effect of an intervention on the study subjects. Examples include positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); disease processes; health-related behavior; and, well-being or quality of life

Throughout this manual, the terms **clinical research study** and **clinical trial** will be used interchangeably.

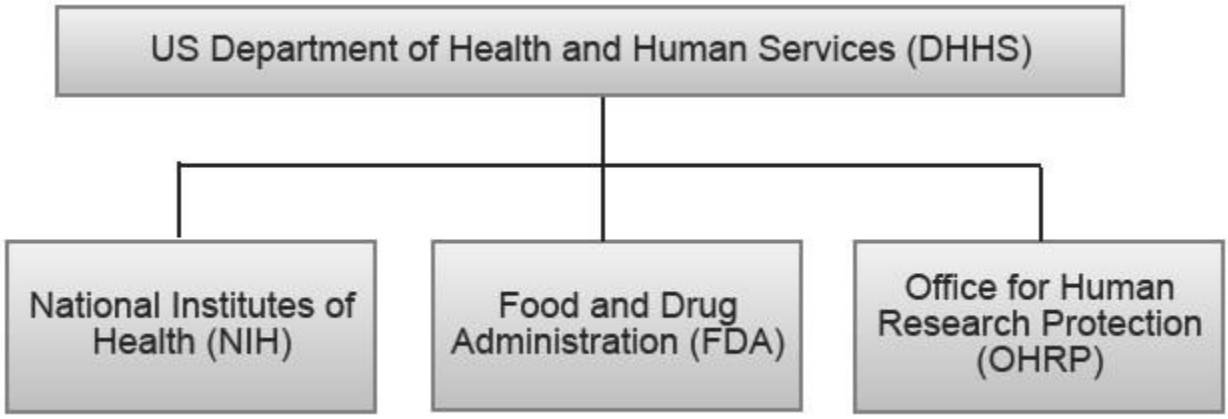
Chapter 1: Basic Concepts in Clinical Research

A. Overview of Clinical Research Regulations and Guidance

Depending on the research study type and the specific funding agency or sponsor, there may be multiple levels of regulatory and compliance oversight, including federal regulations, state laws, institutional policies and guidelines, and funding agency or sponsor policies and guidelines. It is important to understand all of the regulations and policies, as they lay the **groundwork** for and guide the conduct of research studies. Understanding the levels of oversight for a study will ensure the appropriate procedures are in place.

Department of Health and Human Services

The diagram below was derived from the US Department of Health and Human Services (DHHS) organizational chart. The full organizational chart is found online at (http://www.hhs.gov/about/orgchart/).



Most clinical research studies that take place at an Academic Health Center (AHC) are regulated by one or more of the DHHS agencies. Though all these agencies are part of DHHS, they function under different sets of regulations that will be discussed later in this chapter.

Most government agencies have the legal authority to develop and enforce their own specific regulations and rules, including the National Institutes of Health (NIH), the Food and Drug Administration (FDA), and Office for Human Research Protection (OHRP). Such agency-specific regulations and rules are announced in the daily Federal Register and published, or codified, in an annual update to the Code of Federal Regulations (CFR).

The CFR has 50 titles representing broad areas. Each title is further divided into parts that cover specific regulatory areas, for example, 21 CFR 50 is shorthand for Title 21 of the Code of Federal Regulations, Part 50.

The FDA functions under Title 21 and OHRP regulations are included in Title 45.

Office for Human Research Protections

OHRP is the federal office that creates and enforces the regulations for all types of human subjects research, not just clinical research.

In 1974, the Department of Health, Education and Welfare, now known as the DHHS, published regulations for the protection of human research subjects, Title 45 CFR Part 46, the Federal Policy for the Protection of Human Subjects. This regulation became known as the **Common Rule** in 1991 when an additional 14 federal departments and agencies incorporated the policy into their own regulations. That number continues to grow.

The **Common Rule** is applied to biomedical and behavioral research involving human subjects in the United States and is the **basic standard of ethics** to which any government-funded research in the US is held.

Most researchers in academic institutions, including UW-Madison, apply these protections to all types of research involving human subjects.

National Institutes of Health

NIH is located within the DHHS. In addition to conducting its own research studies, the NIH provides federal funding for thousands of researchers in universities through its institutes and centers.

It is important to note that although the NIH is primarily a funding agency and not a regulatory body, research studies funded through the NIH are regulated under 45 CFR 46, the Common Rule, and by the stipulations of the funding grant and institute or center within the NIH.

Food and Drug Administration

The Food and Drug Administration (FDA) is also a branch of the DHHS. The FDA is the regulatory body responsible for the regulation and oversight of human subjects research that involve drugs, devices, biologics and vaccines. These types of studies must adhere to CFR Title 21.

Investigational New Drug (IND) Application

Prior to evaluating a drug in humans, the sponsor must receive approval from the FDA to conduct a study under an investigational new drug application (IND) application. This FDA application process standardizes the testing of new medications with human subjects.

The FDA has two primary objectives in reviewing an IND application

1. To assure the safety and rights of subjects are protected in all phases of a new drug investigation.
2. To assure the quality of the scientific investigation of the drug is adequate to permit an evaluation of the drug's effectiveness and safety.

An **investigational drug** is the object of clinical investigations to determine the **safety and effectiveness** of the drug. The term **investigational drug** in this manual refers to a drug being investigated under an IND application. This includes new drugs and FDA approved drugs being evaluated for a new indication or in combination with other drugs. Investigational drugs and the various stages and phases of development will be described in more detail later in this manual.

When all phases of clinical studies are successfully completed, the holder of an IND Application may then submit a New Drug Application (NDA) to the Center for Drug Evaluation and Research (CDER) for approval of the drug for the indication under investigation. For therapeutic biologics, a Biologic License Application (BLA) is completed and submitted in the same manner.

Investigational Device Exemption (IDE) Application

If the study is evaluating an investigational device, the FDA reviews an investigational device exemption (IDE) application with the same objectives in mind.

It can be counterintuitive to grasp that submitting an IDE application is the process for testing a new device. The term **exemption** means that it doesn't meet the PreMarket Approval (PMA) regulatory requirements, thus it must go through rigorous testing to ensure safety and effectiveness.

The term "device" is very broad and refers to an instrument, apparatus, implement, machine, implant, in vitro reagent, or other similar or related article intended for use in the diagnosis, mitigation, treatment, or prevention of disease. Examples of devices vary widely from bandages, to pacemakers, defibrillators, and infusion pumps. Even wheelchairs and crutches are considered devices.

An **investigational device** is the object of clinical investigation(s) to determine the safety and effectiveness of the device, and is not available for commercial sale or distribution for the indication being evaluated.

When all stages of investigation are successfully completed, the individual that submitted the IDE application to the FDA may then submit a PMA application to the Center for Devices and Radiological Health (CDRH) for approval of the device for commercial sales and distribution.

Investigational devices and the various types, stages and phases of development will be described in more detail later in this manual.

Table 1.

Application Type	Investigational Product		
	Drug	Biologic	Device
Investigational	IND	IND	IDE
Approval	NDA	BLA	PMA

Table 1 provides a summary of the Investigational Product stages, identifying how the different processes correspond to the different types of investigational product.

The definitions below were abstracted from the FDA Glossary of Terms: https://www.fda.gov/drugs/informationondrugs/ucm079436.htm

A **Drug** is defined as:

- A substance recognized by an official pharmacopoeia or formulary, created using a chemical process
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

- A substance (other than food) intended to affect the structure or any function of the body.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

A **Biologic** is defined as:

- Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.
- Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.
- Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies.

In general, the term "drugs" includes therapeutic biological products.

B. Federalwide Assurance

For an institution to accept federal research funding, it must obtain, or hold a **Federalwide Assurance (FWA**). UW-Madison has an FWA to provide assurance to the federal government that investigators working on human subjects research will comply with the **terms of assurance**.

The **terms of assurance** dictate that when an institution engages in FWA-regulated research, the institution assures compliance with the principles of the Belmont Report, the Common Rule, and all other applicable federal, state, institution or funding agency regulations and good clinical practice guidelines.

C. Good Clinical Practice

There are many regulatory authorities involved in the oversight of clinical research as described thus far. In addition, there is one international “gold standard” guideline that, if followed, meets all the regulatory authority oversight expectations - the Good Clinical Practice (GCP) Guidelines.

GCP is an international standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

The FDA accepted the GCP guidelines when they were published in the Federal Register on May 9, 1997. Revision 2 (R2) was adopted by the FDA on March 1, 2018.

D. Research Setting

In addition to the Federal regulations, all members of the research team should be aware of the research setting in which they are conducting research. The steps to initiate, conduct and report research may differ based on the research setting. This manual is geared toward research staff conducting research within UW Health or other UW-Madison clinical research environment.

UW Health, an Academic Health Center (AHC) entity comprised of the UW School of Medicine and Public Health (SMPH), the UW Medical Foundation (UWMF), and the UW Hospital and Clinics (UWHC), including the American Family Children's Hospital (AFCH) and the UW Carbone Cancer Center (UWCCC).

E. Sponsor Types

A study sponsor is an individual, company, institution, or organization with the responsibility for the initiation, management, and/or financing of a clinical trial. There are several types of study sponsors; this manual will utilize two categories: industry sponsor and sponsor-investigator.

Industry Sponsor

An **industry sponsored** study is one that is initiated by a company or organization. They develop the protocol and approach a site or an investigator at a site to participate in a study.

The term **industry sponsor** often refers to a pharmaceutical or biotechnology company. But any funding organization, including a small company, a non-profit organization, or a foundation, designs and develops a protocol and approaches a principal investigator (PI) or study site to be involved in the conduct of a study. In this case, the organization or company that approached the study site is considered the **industry sponsor** and assumes the sponsor responsibilities. When conducting an industry sponsored study, UW-Madison typically participates as one of a number of study sites.

A clinical research organization (CRO) may be contracted by the sponsor to manage some of the tasks related to study initiation or study conduct. To provide oversight, a CRO often sends a monitor to a study site to review study records and data.

Sponsor-Investigator

A **sponsor-investigator** is an individual who both **initiates and conducts** an investigation. The term applies only to an **individual**. This term is not used to describe a company, an organization, or an agency. (ICH GCP E6 1.54, 21 CFR 312.3b, 21 CFR 812.3o)

These studies are also referred to *Investigator-Initiated*. The obligations of a **sponsor-investigator** include both those of a sponsor and those of an investigator.

The investigator often seeks funding or support for such studies from non-profit organizations, foundations, private funding, departmental or institutional funding, or federal agencies. An investigator may also take their idea to a company for funding. However, even if the study is funded by a company or organization, if an investigator initiated the study and developed the protocol, the PI is still a **sponsor-investigator** with additional responsibilities. It is most clear that a PI is a sponsor-investigator when conducting federally funded studies.

A federally funded clinical research study is a peer-reviewed activity sponsored under a broad charter by a government agency. Government or federal agencies that provide funding for research include, but are not limited to:

- The National Science Foundation (NSF)
- The Department of Defense (DOD)
- The Department of Energy (DOE)
- The Department of Transportation (DOT)
- The Department of Veteran's Affairs (VA)
- The National Institutes of Health (NIH within the DHHS)

Within the various federal agencies referenced above, there are also subdivisions. For example, the NIH has 27 institutes and centers that support research whose funding falls within the federally-sponsored category. Examples include, but are not limited to the National Institute on Aging, the National Heart, Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, and the National Cancer Institute (NCI). The various centers and institutes

can have additional categorization. For instance, the NCI has various cooperative groups and consortiums.

F. Study Types

Most researchers categorize study types by the investigational product, such as drug, device, or biologic. However, these products can be used for various reasons, thus we have categorized the studies based on the **intent** of the investigational product.

Intervention

Intervention is a process or action that is the **focus** of a clinical research study. This could include the use of investigational drugs or medical devices, or testing new procedures. Interventions could also include noninvasive approaches such as training and education. Intervention studies have been further divided, as described below.

Therapeutic Intervention

A therapeutic intervention study is one that evaluates the usefulness of investigational therapies compared to standard treatments or no treatment. This could involve an investigational drug, a device, a biologic, gene therapy, radiation therapy, stem cell therapy, or nutritional, behavioral, or psychosocial approaches.

Prevention Intervention

A prevention intervention study is one that looks for better ways to prevent disorders from developing or recurring. Different kinds of prevention research may involve drugs, vitamins, vaccines, minerals, or lifestyle changes.

Supportive Care Intervention

Supportive care intervention studies explore ways to improve comfort and the quality of life for individuals with a chronic illness. Supportive care research may involve drugs, nutritional, behavioral, or psychosocial interventions.

Non-Intervention

There are types of studies that don't involve an intervention, including:

- A genetic study that involves blood tests for genetic analysis related to a disease or condition
- A long-term study that involves psychological tests and brain scans

- A study of family history that involves talking to family members to learn about people's medical needs, their environment, and their history.

The Non-Intervention study type has been further divided, as described below.

Epidemiologic/Observational/Outcomes

Epidemiological studies seek to identify the patterns or contributing causes of disorders in groups of people. Epidemiologic, observational, and outcomes studies could involve healthy populations and diagnosed patients. These studies could include observation or surveillance, surveys, outcomes, or monitoring the subject's environment.

Chart Review

Chart review studies collect data from patient medical records. A chart review study could be retrospective, prospective, or both. An example of a chart review study would be one that collects data from medical records to compare breast cancer patients treated surgically with those that chose radiation therapy only. Another example would be collecting data to compare the outcomes of laparoscopic vs. open surgery techniques.

Registry/Database:

Registry or database studies create individual databases for the collection of data from certain types of subjects. The data to be collected needs to be identified, but the research question may not be known. Examples of registries include a tumor registry, or the Wisconsin Diabetes Registry.

Biospecimen Repository

Biospecimen or biorepository studies involve collection of biological specimens from healthy volunteers and/or diagnosed patients. The specimens may be used in ongoing laboratory studies or may be preserved for future use.

Screening, Early Detection, or Diagnostic

Screening research aims to find the best ways to detect or screen for certain disorders or health conditions. Detection or diagnostic refers to the practice of looking for better ways to identify or diagnose particular disorders or conditions. These studies may look for individuals with certain risk factors, disease types, or individuals who may be showing signs and symptoms of disease.

Other Types of Studies

Extension (Rollover)

Extension or rollover studies are clinical research studies in which the use of experimental therapeutics are extended for a longer period of time. Extension studies are considered a new protocol, even if they are exactly the same as the initial study with different enrollment procedures. Only those subjects enrolled in the initial study may be enrolled in the extension, a rollover of the subjects actively enrolled. Extensions occur to continue providing treatment to patients who are benefitting from treatment during the initial protocol.

Ancillary or Sub-study

Ancillary or sub-studies involve procedures done in addition to the main study to answer additional questions. The ancillary or substudy may be part of a main clinical study or may utilize patient information from the main study in addition to data from additional procedures. For example, an investigational drug study may also collect laboratory samples to analyze the effects of the drug on a certain protein. The purpose of the main study is to evaluate the safety and effectiveness of the investigational drug, while the ancillary or sub-study collects information about the protein.

These studies may be optional or required. In addition, they may either be embedded in the main study, or they may be a completely separate study, requiring a separate protocol and perhaps a separate consent form.

The following study types are common in cancer-related research:

Correlative

Laboratory or radiology based studies utilizing subject specimens for assessment of risk, clinical outcomes, therapy response.

Adjuvant Treatment Studies

Adjuvant studies are additional therapy after standard treatment and are designed to prevent the recurrence of cancer in people who no longer show clinical evidence of disease. Typically, adjuvant studies attempt to treat the subclinical or microscopic disease thought to be responsible for cancer re-occurrence and therefore improve disease-free and overall survival.

Neoadjuvant Treatment Studies

Neoadjuvant studies are additional therapy before standard treatment. Such studies evaluate treatments designed to reduce tumor size to a point where it can be effectively

treated by standard of care therapies. For example, clinical research studies have shown that chemotherapy can reduce an inoperable breast cancer to a size that can be removed surgically.

Compassionate Use or Expanded Access

Compassionate use describes a way to make non-FDA approved drug products available to patients. The intent is to provide treatment to the patients, *not to evaluate the safety and effectiveness of the drug products*. *This process is often confused as research, but is in fact mechanisms to make non-FDA approved drug available for clinical care.*

Under compassionate use, a physician may request access to a drug that is still under development to treat a patient who has exhausted all approved options for a severe or life-threatening disease. The patient is informed that the drug is investigational and not FDA-approved and is given the opportunity to understand the limited knowledge about the risks and benefits of the drug at this stage of development.

The sponsor decides whether to make the investigational drug available to an individual for compassionate use, or to many patients through what is called an **Expanded Access** or **Open Protocol**. The data from compassionate use and expanded access studies are included in the application for FDA review, but since the data are not derived from a well-designed, adequately controlled clinical trial, they are not considered to be pivotal.

G. Phases of Clinical Development

Preclinical or Non-Clinical

The drug development process actually begins with preclinical, or non-clinical research in the laboratory. Non-clinical studies are those that do not involve human subjects. Preclinical or non-clinical studies are necessary to gather information including toxicology, pharmacology, and pharmacokinetics to support clinical research in humans.

Clinical Studies

There are many ways to categorize clinical studies. Investigational device studies are categorized in a slightly different way than investigational drug or biologic studies

H. Investigational Device Studies

As previously referenced, the term "device" is very broad and refers to an instrument, apparatus, implement, machine, implant, in vitro reagent, or other object that is intended for use

in the diagnosis, treatment, or prevention of disease. Examples of devices vary widely, from bandages, to blood pressure cuffs, to pacemakers.

Investigational Devices are categorized as **Significant Risk** or **Non-Significant Risk.**

Significant Risk, Non-significant Risk, Exempt

A **significant risk** device refers an investigational device that is used to support or sustain life and presents a potential for serious risk to the health, safety, or welfare of a subject.

Significant risk device studies must have an IDE application approved by FDA before they may proceed and must follow the FDA regulations described in 21 CFR 812.

A **non-significant risk** device study is one that does not meet the definition of a significant risk device study.

Non-significant risk device studies do not need an IDE application with the FDA, but still must follow the abbreviated FDA requirements of 21 CFR 812. These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, and reports.

An **exempt** device is a diagnostic device, in which the tests are noninvasive and don't require an invasive sampling procedure that could present significant risk. It does not introduce energy into a subject and is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure.

Device studies which are exempt from the requirements of the IDE regulations are not exempt from the regulations requiring IRB review and approval and the protection of human subjects.

Device Classes

Class I General Controls

Class I devices are subject to the least regulatory control. Class I devices are subject to "General Controls" as are Class II and Class III devices. General controls include procedures to control misbranding, device repair, replacement or refund, and good manufacturing practices.

Class I devices are not intended to help support or sustain life or be substantially important in preventing impairment to human health. Most Class I devices are exempt from the premarket process and a few are also exempt from most good manufacturing practices regulation.

Examples of Class I devices include elastic bandages, examination gloves, hand-held surgical instruments, and wheelchairs.

Class II: General controls with special controls

Class II devices are those for which general controls alone cannot assure safety and effectiveness thus additional controls must be applied. In addition to complying with general controls, Class II devices are also subject to special controls. Special controls may include special labeling requirements, mandatory performance standards and postmarket surveillance.

Devices in Class II are held to a higher standard than Class I devices, and are designed to perform as indicated without causing injury or harm to subject or user. Examples of Class II devices include acupuncture needles, powered wheelchairs, infusion pumps, surgical drapes, and implantable radiofrequency transponder systems for patient identification and health information.

Class III: General controls and premarket approval

A Class III device is one for which insufficient information exists to assure safety and effectiveness solely through the use of general or special controls sufficient for Class I or Class II devices. Such a device needs PMA, a scientific review to ensure the device's safety and effectiveness.

Class III devices are usually those that support or sustain human life and are of substantial importance in preventing impairment of human health. Examples of Class III devices include implantable pacemakers, pulse generators, and automated external defibrillators.

Device Categories

Many investigational device studies being conducted under an IDE gather the scientific information needed for the FDA to establish the safety and effectiveness of that particular device. In the past Medicare coverage was **denied** for devices which were under an IDE and had not yet received FDA approval because the treatments were considered experimental. However, there are devices which are refinements of existing technologies or replications of existing technologies made by other manufacturers. The FDA now places devices into two categories to help determine Medicare coverage:

Experimental (Category A)
Experimental devices are innovative devices in which "absolute risk" has not been established. For example, initial questions of safety and effectiveness have not been resolved and thus FDA has not determined whether the device type could be considered safe and effective.

Investigational (Category B)
Studies using investigational devices are expanding the research, based on previous data. This category includes device types that could be considered safe and effective perhaps because other manufacturers have already obtained FDA approval for the device type. Non-significant risk studies may also be included in this category. If the appropriate approvals have been obtained, Medicare may cover the research-related costs associated with Category B devices.

501(k) Clearance
A new medical device that can be demonstrated to be **substantially equivalent** to a previously legally marketed device can be **cleared** by the FDA for marketing as long as certain requirements are met. The vast majority of new medical devices enter the marketplace via this process. The 510(k) pathway rarely requires clinical trials.

I. Investigational Drug Studies

The term **drug** refers to articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases or conditions in humans. The term **investigational drug** refers to a drug being investigated under an IND. This includes new drugs and FDA approved drugs being evaluated for a new indication, in combination with other drugs, or in a new subject population.

The FDA categorizes investigational drug studies into development stages, or phases, based on study characteristics such as the objective and number of participants.

There are five phases: Phase 0, I, II, III, and IV.

Phase 0: (Exploratory)

Phase 0 studies are exploratory and involve very limited human exposure to the drug, with no therapeutic or diagnostic goals.

Phase I: (Human Pharmacology)

Phase I is the first step in testing a new drug in humans after animal research. Researchers evaluate the treatment's safety, determine a safe dosage range, and identify side effects. These studies test the best way to give a new treatment, the route of administration, and the best dosage. The dose is typically increased a little at a time to find the highest (maximum) dose that does not cause harmful side effects.

Because little is known about the possible risks and benefits of the treatments being tested, Phase I trials usually include only a small number of subjects, typically healthy controls. These studies monitor adverse events closely, including their severity and frequency.

Though Phase I studies are primarily concerned with assessing a drug's safety, they are also done to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness.

Phase I studies typically include a small number of healthy volunteers. Phase I studies could also enroll a small number of diagnosed patients who have not been helped by other treatments. Phase I studies usually brief in duration.

Phase II: (Therapeutic Exploration)

Phase II studies are controlled clinical studies to gather preliminary data on effectiveness, and to determine if the drug works as predicted in people who have a certain disease or condition. For example, participants receiving the drug may be compared with similar participants receiving a different treatment, which may be either an inactive substance, called a placebo, or a different drug.

This phase could take several months to years to evaluate the drug's therapeutic effect, dose range, and metabolism. During this phase, the goal is to minimize toxicity, maximize therapeutic effect, and assess populations of patients who may benefit or be adversely affected when taking the medication. This phase also identifies common short-term side effects and risks.

In Phase II studies, the investigational product or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

Phase II studies typically last 1 – 2 years, longer than a Phase I study.

Phase III: (Therapeutic Confirmatory)

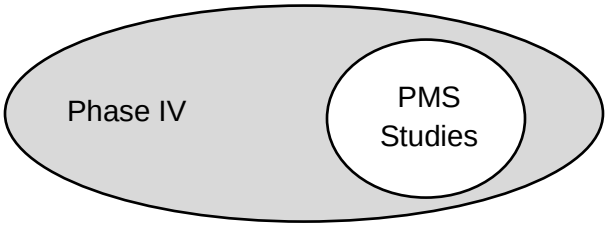
Phase III studies that gather more information about safety and effectiveness by studying different populations and different dosages. These studies are often referred to as **Pivotal**, as they provide primary evidence for the FDA submission. These studies also focus on the validity of the study endpoints and long term safety.

The study drug is given to large groups of people in the target patient population with the a specific disease/condition. Researchers confirm effectiveness, monitor side effects, and compare to commonly used treatments.

Phase III studies typically last longer than two years to gather long term safety data.

Phase IV: (Therapeutic Use)

Phase IV studies are conducted after FDA approval has been obtained to provide additional information about treatment risks, benefits, and best use. These include post-marketing surveillance (PMS) studies. Not all Phase IV studies are PMS studies, but every PMS study is a Phase IV study.



PMS studies may be mandated by the FDA to further investigate certain aspects of an intervention or procedure. If a PMS study reveals a safety issue, the FDA must determine the appropriate action, which could include adding information to product labeling, restricting use or distribution, or removal from the market.

Phase IV studies gather additional information about the drug's effects in different segments of the population by enrolling a more diverse group of subjects. Phase IV studies also gather additional information used to determine cost effectiveness, drug compliance, or the drug's impact on quality of life.

Dietary Supplements

Dietary supplements are not drugs, but rather compounds that do not make health claims regarding the treatment of a specific disease or condition and are therefore regulated as foods by the FDA. The FDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering conventional foods, prescriptions, and over-the-counter drug products.

Many people sometimes find it difficult to distinguish between a drug and a dietary supplement. If a product is approved by the FDA based on evidence that it was safe and effective for treating a disease, it is regulated as a drug; however, if a product does not make claims to treat, cure or mitigate a disease and only makes claims to **improve overall health**, a broader, more vague statement, it is regulated as a dietary supplement.

J. Study Design

The general study design describes the strategy by which interventions are assigned to participants in a clinical study. This chapter will not go into significant detail, but rather give a broad overview so all members of the study team have a general understanding of the study design. This will allow the research support staff to interact with study participants more effectively by allowing them to adequately describe the study design to the research subjects.

There are several types of intervention models, including Single group design, Parallel design, Crossover design, and Factorial design.

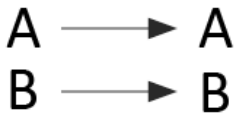
Single Group

Single Group design describes a clinical research study in which all subjects receive the same intervention throughout their participation in the study.



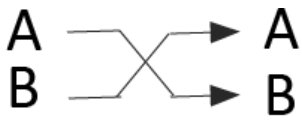
Parallel

Parallel design describes a study in which two or more subject groups receive different interventions at the same time, in parallel. For example, a two-arm parallel design study involves two groups of participants. One group receives drug A, and the other group receives drug B throughout their participation. Hence, participants in one group receive drug A "in parallel" to participants in the other group receiving drug B.



Crossover

In a crossover study design, subjects are given one treatment and then "crossover" to another treatment. For example, a two-by-two crossover design involves two groups of participants. One group receives drug A first, then switches to drug B. The other group starts drug B, then switches to drug A. All participants receive drug A and drug B at some point during the study, but in a different order, depending on their assigned group.



Factorial

Factorial design describes a clinical study in which groups of participants receive one of several combinations of interventions. For example, a two-by-two factorial design involves four groups of participants. Each group receives a combination of 2 interventions. The first group receives drug A and drug B, the second group receives drug A and placebo, the third group receives placebo and drug B, and the fourth group receives placebo and placebo. During the study, all possible combinations of the two drugs, A and B, and placebo are given to different groups of participants.

A, B	Placebo, B
A, Placebo	Placebo, Placebo

Controlled vs. Uncontrolled

A controlled study assesses a group of subjects receiving the investigational treatment against a control group of subjects that does not receive the treatment. This comparison group gives investigators important clues about the effectiveness of the treatment and its side effects.

The most common type of study in this design is a placebo-controlled study comparing one or more active treatment groups to a placebo group that does not receive the active treatment.

Single or Multiple Dose/Fixed or Variable

Some studies look at one or more treatments, or doses, in comparison to each other. The various treatments and/or doses used should be outlined in a detailed protocol for study coordinators.

Single Site or Multi-Center

Some clinical research studies are conducted at a single site, while multi-center studies are conducted at more than one study site. The protocol will indicate whether it is a single or multi-center study.

Blinded or Unblinded

Open Label or Unblinded

In **Open Label**, or **Unblinded** studies, the subject *and* the investigator know which treatment the subject is receiving. Sometimes the treatment cannot be blinded, particularly in surgical technique studies in which the investigator knows which surgical technique was used and it may not be possible or ethical to hide the specific treatment from the patient.

Blinded: Single-blind

In a single-blind trial, either the investigator or the subject knows the details of the treatment. In practice, if one of them know the treatment that is being recieved, it is possible for them to subconsciously relay important treatment-related details, thus influencing the study outcome.

Blinded: Double-blind

In a double-blind trial, interventions are randomly assigned to subjects, and neither the subject nor the investigator knows the treatment assignment. Consequently, the study staff cannot convey information about the study treatment, intentionally or unintentionally. Therefore double-blind, or “randomized.” studies are preferred, as they limit the potential for bias.

The blind should be maintained at all times. There are procedures to be followed if the blind must be broken for subject safety reasons.

Blinded: Double Dummy

Double dummy is a technique for retaining the blind when two treatments cannot be made identical. For example, Drug A can only be administered in liquid form and Drug B can only be administered in tablet form. Every subject will take two sets of treatment. Using this example, the subjects could receive:

- Active liquid and active table,
- Active liquid and placebo tablet,
- Placebo liquid and active tablet, or
- Placebo liquid and placebo tablet.

Randomization

Randomization is a method used to prevent bias in research. The randomized study is widely considered the most reliable form of scientific evidence because it is the best known design for eliminating the variety of biases that could compromise the validity of the research. In a randomized study, a computer or table of random numbers determines the treatment assignments and participants have an equal chance to be assigned to one of the groups.

There are several potential types of randomization and the study protocol will identify the type of randomization, if applicable. It is important to have a basic understanding of the randomization process to be able to explain the different ways and likelihood that subjects could receive various treatment options.

Block randomization

Block randomization is the arrangement of treatment options within groups, or blocks. The treatments are randomized within each block to avoid potential imbalance.

1	A
2	B
3	A
4	B

5	B
6	B
7	B
8	A

9	B
10	A
11	B
12	A

13	A
14	A
15	B
16	B

Stratified

Stratification is used to allow the researchers to further refine the groups in which subjects will be placed. For example, individuals could be divided up into two groups, such as women and men, and then randomized to their treatment.

Example:

Women		Men	
A	1	B	1
B	2	B	2
A	3	A	3
B	4	A	4
B	5	B	5
A	6	A	6
B	7	A	7
A	8	B	8

Chapter 2: UW-Madison Clinical Research Infrastructure and Corresponding Policies

This module provides a brief overview of the entities involved in the oversight of clinical research at the University of Wisconsin-Madison (UW-Madison). Clinical research at UW-Madison is supported by many diverse entities that vary greatly in size and scope. Some entities' policies and procedures affect all researchers, while other entities' policies and procedures only apply to those engaged in specific types of research. Not all researchers come in contact with all of the offices or committees described in this chapter, but all those involved in clinical research should be aware of the role that each plays.

A. Human Research Protection Program

The Human Research Protection Program (HRPP) provides oversight of all research activities involving human subjects at the UW-Madison. The HRPP is not an office, but rather a collective effort of all who participate in the conduct, review, approval and facilitation of Human Subjects Research at UW-Madison. The HRPP is staffed by the Office of Research Compliance to maintain the university's policies governing human subjects research, which apply federal, state and other regulatory requirements to all university faculty, staff, students, volunteers and research subjects. Refer to Section E later in this chapter for more information.

The HRPP policies address the review, approval and conduct of human subjects research at UW-Madison. Some prominent issues addressed by these policies include the definition of human subjects research, the principal investigator (PI) status for human subjects protocols, the use of existing datasets, and applying state law. The UW-Madison HRPP Policies are available on the HRPP homepage in a index and are searchable by full-text and keyword.

https://research.wisc.edu/compliance-policy/human-research-protection-program/

B. UW-Madison Institutional Review Boards

UW-Madison's Institutional Review Boards (IRBs) are one of the largest components of the HRPP. UW-Madison has three separate IRBs - the Health Sciences (HS) IRB, the Health Sciences Minimal Risk (MR) IRB, and the Education and Social/Behavioral Sciences (ED/SBS) IRB. Researchers send their human subjects protocols to the appropriate IRB based on the nature of research project. IRB-specific policies and procedures can be found on their websites included later in this chapter.

Health Sciences IRB

(https://kb.wisc.edu/hsirbs/)
The HS IRB reviews research protocols involving medical interventions or procedures where medical expertise is required for evaluation.

Health Sciences Minimal Risk IRB

(https://kb.wisc.edu/hsirbs/)
The MR IRB reviews research protocols that present minimal risk to subjects and involve medical interventions, procedures requiring medical expertise, or knowledge of the healthcare setting, (i.e. medical records research, research database and tissue banking projects, survey and interview research, and exemption applications).

Education and Social/Behavioral Science IRB

(http://www.irb.wisc.edu/)
The ED/SBS IRB primarily reviews education, social, behavioral, and non-medical health research. The ED/SBS IRB does review some minimal risk health-related studies, (i.e. studies involving exercise, tape sensors, and single venipuncture) where medical training is not necessary to evaluate the risks to research participants.

UW-Madison IRBs may also agree to defer to another institution's IRB, or a central IRB. UW-Madison routinely defers to the **Western IRB (WIRB)** and the **National Cancer Institute's Central IRB (CIRB).** UW-Madison is also part of the Wisconsin IRB Consortium, referred to as WIC. WIC is an agreement among 4 institutions – Aurora Health Care, Marshfield Clinic, Medical College of Wisconsin, and the University of Wisconsin-Madison. This agreement allows WIC institutions to defer IRB oversight to a single WIC member IRB for studies that involve 2 or more WIC institutions. Information on how to defer to these IRBs is found on the HS IRB office website (https://kb.wisc.edu/hsirbs/).

C. UW Institute for Clinical and Translational Research

The NIH-funded UW Institute for Clinical and Translational Research (ICTR) is composed of five academic partners at UW including the Schools of Medicine and Public Health, Nursing, Pharmacy, and Veterinary Medicine, and the College of Engineering. Also part of the UW ICTR partnership is the Marshfield Clinic Research Foundation located in Marshfield, Wisconsin. ICTR supports a number of key research services and infrastructure important for conducting clinical and translational research (https://ictr.wisc.edu).

D. Scientific Review Committees

All studies submitted to the HS and MR IRBs are required to undergo scientific review prior to IRB review (https://kb.wisc.edu/hsirbs/page.php?id=18844). There are two UW-Madison Scientific Review Committees (SRCs):

- UWCCC Protocol Review Monitoring Committee (PRMC)
- UW ICTR Scientific Review Committee (SRC)

Studies reviewed by one UW-Madison SRC will not be reviewed by the other. Review and approval by an SRC is separate from IRB review, and SRC approval is required *prior* to IRB review of the study. The UWCCC PRMC is a NCI-mandated SRC for all cancer-related research protocols. The ICTR SRC reviews non-cancer related studies that have not otherwise undergone scientific peer review by an entity such as NIH, the Veteran's Administration (VA) or industry sponsor. Industry-sponsored studies deferred to WIRB are also exempt from the SRC requirement.

The ICTR and UWCCC SRCs review projects for scientific merit and validity in the following areas:

- Study Rationale
- Subject population
- Study Objectives
- Study Outcomes
- Preliminary Data/Literature
- Scientific Merit
- Study Design and planned treatment(s)
- Statistical Considerations (sample size/justification, estimated accrual and duration, and proposed data for analysis)
- Data and safety monitoring plan

In addition, the UWCCC PRMC also reviews studies for:

- Potential conflict of interest
- Prioritization of protocol with other studies utilizing the same patient population
- Feasibility of attaining stated goals

E. Office of Research Compliance

In addition to supporting the HRPP, the Office of Research Compliance (https://research.wisc.edu/compliance-policy/human-research-protection-program/) coordinates and facilitates research policy, ethics, and compliance activities for research conducted across the UW-Madison campus. This includes support for the following research-associated programs. More information on the responsible conduct of research, research misconduct, conflict of interest, and stem cell oversight can be found using the links on the HRPP homepage.

Responsible Conduct of Research (RCR)

An additional eight hours of training focusing on responsible conduct of research (RCR) may be required for certain researchers, including, but not limited to, those receiving NSF funding, training grants, or certain NIH grants, and those participating in US Department of Agriculture research. The specific training may vary based on the agency or department funding the research. Refer to the Responsible Conduct of Research website for more information: https://research.wisc.edu/kb-article/?id=34483

Research Misconduct

At UW-Madison, misconduct in scholarly research is defined as fabrication (making up data), falsification (changing or misreporting data), plagiarism (representing work of others as one's own), or other practices that seriously deviate from those commonly accepted within the scholarly community for proposing, conducting, or reporting research. UW-Madison has adopted a federally-mandated three-phase phase process for investigating allegations of research misconduct. This process consists of an inquiry phase, a Chancellor's review, and a hearing phase. Refer to Faculty Policy II-314 and the Research Misconduct website (https://research.wisc.edu/kb-article/?id=34484) for more information.

Conflict of Interest and Outside Activities Reports

The UW-Madison encourages faculty, staff, and students to engage in outside activities and to share their knowledge and expertise. UW acknowledges that potential financial conflicts of interest (COI) may result and are common, often unavoidable, and not necessarily problematic. UW-Madison has a COI Committee comprised of faculty members from across campus to review Outside Activity Reports (OAR) submitted by all faculty and academic staff for potential financial conflicts of interest. Prompt submission of the OAR will help expedite any protocol submissions or grant proposals made before the next annual reporting period. The COI policies,

guidance, and information on how to submit the OAR are located on the COI Program website (https://research.wisc.edu/compliance-policy/outside-activities-reporting/).

Stem Cell Research Oversight (SCRO)

The Stem Cell Research Oversight (SCRO) committee provides oversight for all research on campus involving: the use of human embryonic stem cells or their derivatives; or the introduction of human pluripotent stem cells, or their derivatives, obtained from a non-embryonic source, into non-human animals at any embryonic, fetal, or postnatal stage, if an expected effect is that human cells will be integrated into the central nervous system, testes, or ovaries of the animal. There are separate training requirements for researchers involved in the types of stem cell research described above. The SCRO policies, guidance and training information are located on the SCRO website (https://research.wisc.edu/compliance-policy/stem-cell-research-oversight-committee/).

F. UW Health Policies (UW Hospital and Clinics and UW Medical Foundation)

UW Health provides an environment for the conduct of clinical research. The investigator and the members of the research team are required to follow all UW Health policies and procedures when conducting research within UWHC or UWMF clinical space, in addition to following the Health Link Documentation Guidelines for research related activities/care. These policies apply to students, providers, volunteers, and staff.

Overall Guidelines

UW Health policies can be accessed through the UConnect webpage (https://uconnect.wisc.edu) by clicking on the policies button in the navigator toolbar at the top of any UConnect webpage. Access to the internal UConnect website is restricted. Investigators or research staff who are unable to access UWHC policies through UConnect should contact the department or unit manager where the research will be conducted to assist them in obtaining appropriate policies. The following is a list of UWHC policies that commonly apply to clinical research; however this is not an exhaustive list.

- **UWHC 4.24: Clinical Research Guidelines**
  This policy requires individuals interested in conducting research involving human subjects to obtain either approval of or an exemption from the appropriate IRB approved by UW, prior to the initiation of such research.

- **UWHC 12.10: Research Safety Committee Authority & Function**
  This policy describes the additional review and approval necessary when a clinical (human) research study possessing potential health hazards is identified that could pose potential safety concerns to employees that are not adequately covered by existing policies. Such protocols include those involving gene therapy, infectious agents, and other novel therapies.

  Any clinical research protocol that requires Institutional Biosafety Committee (IBC) approval will require submission and approval by the Research Safety Committee (RSC). RSC approval is required before IRB approval may be issued. RSC approval is granted on a per protocol basis and NOT on a per agent basis

Additional Policies related to Clinical Research

Organization	Policy #	Policy Title	Brief Description
UWHC	6.39	Legal Medical Record	Defines elements that comprise the legal medical record for UWHC.
UWHC	6.15	Medical Record Documentation	Defines medical record documentation requirements.
UWMF	MF	Patient Medical Record	To provide direction for timely, accurate documentation of patient encounters in order to facilitate continuity of care as well as comply with legal responsibilities.
UWHC	2.13	UWHC Charges for Patients in Research Studies	This policy describes the UWHC billing policy and procedure for patients participating in research studies. *Refer to Chapter 11: Clinical Research Resources for more information related to research billing.*
UWHC	2.05	Research Diets	This policy provides guidelines for procuring, preparing, and delivering meal trays for research diets.
UWHC	3.11	Research: Obtaining Nursing Resources and Support	Gaining access to nursing time and resources within UWHC

Clinical Research Studies Involving Drugs

These policies describes the Pharmaceutical Research Center (PRC) as the responsible party for coordinating and overseeing all clinical drug research conducted within UWHC facilities, regardless of FDA status.

Organization	Policy #	Policy Title	Brief Description
UWHC	10.1	Pharmaceutical Research Center Goals and Objectives	
UWHC	10.2	Pharmaceutical Research Center Protocol Initiation	
UWHC	10.4	Pharmaceutical Research Center Distribution of Research Drugs/Supplies	
UWHC	10.8	Pharmaceutical Research Center External Sponsor/Agency Audits	Procedure for external sponsor and /or agency audits of clinical drug research protocols handled by the Pharmaceutical Research Center.
UWHC	4.11	Investigational and Study Drug Control	
UWHC	4.27	Compassionate Use of an Investigational Agent or Use of an Investigational Agent from a Second Institution	

Access and Use of Information and Data

Organization	Policy #	Policy Title	Brief Description
UWHC	1.02	Access to Electronic Information Systems	Includes policy on research access
UW Health	---	UW Health Information Sharing Policy	Requesting information from the UW Health Decision Support, ITS Reporting Team, Quality Improvement & Finance Departments
UW Health	1.49	Access to Enterprise Data for Analytics	
UWMF	018	Minimum Necessary Use and Disclosure Policy & Guidelines	Standards to ensure that the minimum necessary protected health information is disclosed when there are reasonable requests or inquiries.
UWHC	4.13	Using and Disclosing (or Releasing) Protected Health Information	Guidelines on the appropriate measures to take when using and/or disclosing/releasing patient health information.
UWMF	019	Accounting of Disclosure Policy & Guidelines	
UWMF	MF	Release & Disclosure of Patient Protected Health Information	

Access and Use of Information and Data (continued)

Organization	Policy #	Policy Title	Brief Description
UWMF	MF 10	Authorization Use	Guidance on written patient authorization for certain uses and disclosures of patient's protected health information
UWHC	4.15	Videotape Recording & Patient Photographs (includes rules when done for research purposes)	
UWMF	MF	Guidelines for Using Photographic Patient Health Information	
UWMF	006	Security & Privacy of Faxed, Printed and Copied Documents	
UWMF	014	Verification Policy	Required safeguards to prevent inappropriate disclosure of patient health information to third parties.

General Policies

Organization	Policy #	Policy Title	Brief Description
UWHC	4.34	Patient Rights and Responsibilities	
UWMF	MF	Guidelines for Ethical and Professional Behavior	
UWHC	3.23	Conducting Nursing Research at UWHC	
UW Health	1.48	UW Health Non-Physician Observer Policy	Onboarding requirements for non-employees to observe, tour, etc., including those for research personnel.
UW Health	11.19	Regulation of Vendor Representatives and the Vendor Liaison Office	Includes registration of vendor representatives involved in research, including study monitors. Also refer the UWHealth page with instructions for research personnel to register a vendor liaison (http://www.uwhealth.org/about-uwhealth/instructions-for-research-personnel/11109).
UWHC	13.15	Use of Containers for Clinical Specimens (includes specimens transported off site for research)	
UWHC	12.33	Handling of Animals for Treatment or Research	

Organization	Policy #	Policy Title	Brief Description
UWHC	1.30	Photo Identification Badge and Security Access Systems	This policy describes the requirements for Photo ID. Badges must be worn by all UWHC employees, volunteers, vendors and service representatives, faculty, i.e., physicians, pharmacists, and nurses, and those using the institution for clinical experience or clinical research, e.g., students.
UWMF	MF	Photo Identification Badge and Security Access Systems	
UW Health	9.16	UW Health Dress Code and Appearance Policy	This policy establishes a dress code and appearance policy for employees who work in locations where clinical care is provided. This policy outlines the minimum acceptable standard for dress and appearance.
UWMF	MF	Standard Precautions	To protect healthcare workers and patients from transmission of any potential pathogen.
UWHC	13.01	Restrictions on Food and Beverage Consumption	Includes policy for patient care areas and research labs.
UWHC	13.08	Hand Hygiene	These policies describe the purpose and process to assure the good hand hygiene to reduce the number of transient pathogens on the hands and the incidence of healthcare-associated infections. Frequency of hand hygiene is determined by the nature of one's activities, length of procedure, and materials handled.
UWMF	MF	Hand Hygiene	

Employees of the School of Medicine and Public Health can refer to the SMPH Intranet, Policies and Procedures webpage for more information: http://intranet.med.wisc.edu/policies-and-procedures/main/30845

For pdf version of the list, go to https://kb.wisc.edu/ictr/page.php?id=44399 (NetID required to access).

Additional Guidance Documents

The following guidelines specific to research are also available on UConnect. Key word searches can be the most rapid way to access these guidelines and Frequently Ask Questions:

- Health Link Documentation Guidelines for Research Related Care
- 21 CFR Part 11
- Research in Health Link
- Stigmatizing Study Guideline
- Research in Health Link
- External Monitors

G. Additional Entities researchers should be aware of:

UW-Madison, Division of Business Services, Accounting Services

The Division of Business Services governs compensation payments to subjects. If subjects will be compensated for study participation, the study team should review the policy on Payments to Individuals (http://www.bussvc.wisc.edu/acct/policy/pir/pirpol.html).

Office of Research and Sponsored Programs (RSP)

No contracts or agreements may be signed solely by the PI and cannot be finalized until reviewed and negotiated by the appropriate office, and signed by an authorized signatory of the University. Depending on the agreement type, the document will be reviewed by RSP or the Office of Industrial Partnerships (OIP) as described below.

All research proposals, contracts, grants, and cooperative agreements with **extramural sponsors**, funding organizations other than UW-Madison, must be routed to the Office of Research and Sponsored Programs (RSP) via the researcher's department and affiliated dean's office. Agreements subject to RSP review include clinical trials, confidential/non-disclosure, research, material transfer, licensing/software/equipment, data sharing, and interagency personnel assignments, along with any amendments, modification, and extensions to the above agreements.

RSP performs the final review of federal, state, and non-profit project proposals for UW-Madison and transmits the proposals to those extramural sponsors. RSP is also an authorized signature authority able to accept awards on behalf of The UW Board of Regents. They are the entity responsible for negotiating language in the funded research agreement/contract with federal, state, and non-profit sponsors, interpreting sponsor policy, and negotiating the indirect cost rate. RSP also provides financial assistance, e.g., preparing financial reports, submitting invoices, and processing payments, and provides other services addressing primary administrative functions including audits and policy.

Information on RSP's policies and procedures can be found on the RSP website (https://www.rsp.wisc.edu/).

Office of Industrial Partnership

The Office of Industrial Partnership (OIP) assists UW-Madison researchers in establishing and nurturing partnerships with private industry. OIP is responsible for the institutional review and signature of industry-sponsored research proposals, as well as a variety of related contractual

agreements. OIP also creates, negotiates, and finalizes the subsequent agreements and ensures that these collaborations remain consistent with the University's mission. The types of agreements handled by OIP include, but are not limited to, memoranda of understanding, non-clinical trial-related confidentiality or non-disclosure, all incoming and outgoing material transfer, data use, and fee-for-service agreements.

Institutional Biosafety Committee

The Institutional Biosafety Committee (IBC) is managed through the UW-Madison Office of Biological Safety. The IBC reviews and approves all UW-Madison research involving the use of recombinant DNA and infectious agents (plant, animal, and human).

Radioactive Drug Research Committee (RDRC)

The primary purpose of this committee is to review and oversee any clinical research study involving radioactive drugs where no IND application is required.

The FDA classifies radioactive drugs into two groups: (1) new drugs requiring an IND (21CFR312) for investigational use, and (2) drugs that are generally safe and effective when administered under the conditions specified in Radioactive Drug Research Committee (RDRC) regulations (21CFR 361.1). In addition to the initial protocol review and approval, the RDRC must review and approve all protocol amendments. Adverse events (AE) related to the radioactive drug must be reported to the RDRC. When RDRC review is required, approval must be obtained before the HS IRB will review and approve the protocol.

Radiation Safety

The Office of Radiation Safety provides information and training for use of radiation emitting materials, devices, or instruments, and waste handling. This includes both ionizing radiation and non-ionizing (electromagnetic) radiation. This office is responsible for radiation safety training, provision of radioactive materials, dosimetry, radioactive waste handling, etc.

The University Radiation Safety Committee administers UW-Madison's radioactive license. All radioactive material use and research must be approved by the committee prior to using such material. All individuals authorized to use radionucleotides must be licensed and meet certain qualifications.

Laboratory Safety

Many activities involving research with human subjects include activities conducted in a laboratory setting or require staff to handle, process, and/or package and ship biological materials and potentially infectious substances. When engaging in these activities, there are additional training requirements, including Bloodborne Pathogens, Occupational Health, and HazMat training. Refer to the Clinical Research Toolkit (https://ictr.wisc.edu/clinical-research-toolkit/) for a new employee orientation and training checklist for a list of all training requirements and links to access more information.

Laboratory safety resources and requirements vary depending on the scope of the research being conducted. The Department of Environment, Health and Safety has several units that provide consultation services, training and compliance resources.

Chapter 3: Roles and Responsibilities of Research Team Members

A. Working as a Member of a Research Team

Effective Teamwork

The conduct of clinical research is a team effort. The foundation of a successful team is communicating effectively, trusting fellow team members, and valuing the skill and knowledge that each member brings to the team. Success of the team is interdependent. Each person has a piece of the puzzle; if even one small piece is missing, the puzzle is incomplete. At a minimum, without each person's contribution, the quality of the product will be far less than that possible when all team members are fully engaged to accomplish the goals and objectives of the project.

Qualities of a Highly Functioning Team

- Interdependence
- Trust
- Higher quality end product
- Efficiency
- Continuous and ongoing evaluation for further refinement

Requirements for a Successful Team

- Knowledge of the resources required for project completion
- Identifying the skills necessary for a successful project
- Involving all stakeholders
- Establishing effective communication procedures

Strategies of a Successful Team

- Involving others in decisions that will ultimately affect them
- Keeping everyone on the team informed of what is going on
- Seeking diverse viewpoints
- Appreciating unique points of view
- Making a conscious effort to listen to and learn from others
- Incorporating all relevant viewpoints into a project

Essentials of Fostering Collaboration

- Creating a climate of trust: show trust to build trust
- Facilitating relationships to initiate interaction
- Saying "we," asking questions, listening, and taking advice
- Identifying skills and knowledge of each team member
- Clearly establishing the responsibilities of each team member

Strategies of a Successful Team

- Knowing that team members can rely on each other will make work less stressful. Asking others for help opens the line of communication and they may in turn ask for help in the future. Never asking for help can isolate team members from each other.
- Collaborative solutions are higher quality, longer lasting, and less prone to error.

B. Communication is Key

Conducting a research study involves interactions between the research team, clinical care providers/staff (if applicable),the sponsor, research administrative offices, ancillary services staff, and research participants. Continually building upon these relationships will foster positive outcomes and help ensure research integrity.

C. Members of the Research Team

There are many members of the research team, often representing different areas of expertise, who work together to conduct a clinical research study and obtain protocol-defined data. Each member of the team must work with a wide variety of people, having a variety of backgrounds and knowledge. All members of the research team have common goals; adherence to regulations, maintaining integrity of the research data, and protecting the rights and welfare of subjects. It is important to understand everyone’s roles, responsibilities, and limitations.

There are also institutional resources and committees that will be involved at different levels with the research done in the institution. It is important to be aware of and know about these groups. Additional information about these entities was discussed in Chapter 2 of this manual.

Principal Investigator

Investigator is an individual who conducts a clinical investigation, under whose immediate direction the investigational product is administered or dispensed to a subject (21 CFR 312.3(b), 21 CFR 812.3(i), ICH GCP E6 1.34). In the event an investigation is conducted by a team of individuals, the **Investigator** is the responsible leader of the team, and may be referred to as the **Principal Investigator (PI)** or Clinical Investigator (CI).

The PI assumes ultimate responsibility for protocol conduct at his/her study site(s).

Who can serve as the PI at UW-Madison?

Individuals with faculty or Clinical/Health Sciences (CHS) appointments qualify as PIs by the nature of their appointments. Individuals with other appointments may be able to serve as PI under certain circumstances. Refer to the institutional policies to learn more about other staff appointments eligible for PI status on the IRB protocol submission.

NOTE: Having PI status on a grant application is not the same as having PI status for human subjects protocols reviewed by an IRB (refer to the PI Status for UW-Madison Human Subjects Protocols policy for more information: https://research.wisc.edu/kb-article/?id=29557).

When conducting clinical research involving the use of drugs, including biological products, under 21 CFR part 312 and the use of medical devices under 21 CFR part 812, the overall responsibilities of the investigator include:

- Ensure that a clinical investigation is conducted according to the investigational plan (referred to as the protocol), the signed investigator statement or agreement and applicable regulations.
- Protect the rights, safety, and welfare of subjects under the investigator's care.
- Maintaining adequate records regarding the receipt, use and disposition of investigational drugs, biologics, or devices used in a research study (21 CFR 312.60, 21 CFR 812.100).

Specific responsibilities of the PI include, but are not limited to:

- Complying with the principles of the Belmont Report and adhering to the regulations outlined in The Common Rule and other applicable regulations, such as the FDA.
- Providing adequate training to and oversight of study personnel and, in the case of clinical research, ensuring protocol procedures comply with GCP requirements.
- Obtaining written documentation of IRB approval or exemption of the study prior to initiating human subjects research.

- Ensuring that legally-effective informed consent is obtained, using an adequate and appropriate consent process, and ensuring the consent process is documented appropriately (unless the IRB has granted a waiver of informed consent or documentation of informed consent).
- Ensuring permission for the use and disclosure of protected health information is obtained in compliance with the HIPAA privacy rule, if the research staff is within the Health Care Component or part of the affiliated covered entity.
- Ensuring compliance with IRB approval conditions, which includes following the procedures and using only the materials within the IRB-approved application and protocol. In the case of exempt human subjects research, monitoring for changes that could alter the exemption determination and consulting with the IRB as necessary.
- Obtaining IRB approval prior to implementing changes of protocol and promptly reporting changes of protocol.
- Submitting continuing review progress report(s) in a timely manner.
- Reporting unanticipated problems (UPs) to the IRB.
- Reporting noncompliance to the IRB.
- Ensuring adequate medical oversight for clinical research studies.
- Ensuring adequate records are kept to document study procedures and adherence with the IRB-approved application and protocol, as well as ensuring records are retained and accessible for the required retention period.
- Registering studies and providing updated information to ClinicalTrials.gov, when required.
- Filing and updating OAR, disclosing relevant potential financial COI to the IRB, and following any management plans for human subjects research issued by the campus COI Committee.
- Ensuring that additional procedures are in place for investigator-initiated, multi-center studies.

PI may delegate tasks, but not responsibilities.

The information in this section was taken from the FDA Guidance on Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf.

PIs that conduct clinical research studies involving the use of drugs and biological products (under 21 CFR Part 312) and medical devices (under 21 CFR Part 812) commit themselves to personally conduct and/or supervise the investigation.

The principal investigator is the person ultimately responsible for the legal and ethical conduct of the study in accordance with the protocol, signed investigator agreement(s), and applicable regulations.

It is common and acceptable practice for investigators to delegate certain study-related tasks to research staff, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated.

The PI is responsible for providing adequate supervision and ensuring tasks are performed in accordance with the protocol and regulations. This responsibility cannot be delegated. Per the FDA Guidance on Investigator Responsibilities, when "assessing the adequacy of supervision by an investigator, (the) FDA focuses on four major areas: (1) whether individuals who were delegated tasks were qualified to perform such tasks, (2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study, (3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and (4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible." [FDA Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf]

Certain tasks may be delegated to members of the study team who are qualified by education, training, experience, and applicable licensure to perform those tasks. The required qualifications depends on what tasks are being delegated. Appropriate delegation is primarily a concern when delegating that that are clinical or medical in nature, such as evaluating clinical response to an investigational therapy in study subjects, e.g., global assessment scales, vital signs, or providing medical care to subjects during the study. Most clinical or medical tasks require formal medical training and may also have licensing or certification requirements. Licensing requirements may vary by jurisdiction, e.g., states, countries. Investigators should consider qualifications/licensing requirements when delegating specific tasks. In all cases, a qualified physician (or dentist as applciable) should be responsible for all research-related medical (or dental) decisions and care.

The FDA Guidance on Investigator Responsibilities [FDA Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects; http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf] lists several "instances in which study tasks have been delegated to individuals lacking appropriate qualifications", some of which are described below.

Examples of tasks that have been inappropriately delegated include:

- Screening evaluations, including obtaining medical histories and final determination if the subject meets inclusion/exclusion criteria
- Physical examinations
- Evaluation of adverse events
- Assessments of primary study endpoints
- Obtaining informed consent"
- Invasive sample or specimen collection, i.e., biopsy

Sponsor-Investigator

A **Sponsor-Investigator** is an individual who *both initiates and conducts* an investigation, under whose immediate direction the investigational product is administered or dispensed (21 CFR 312.3(b), 21 CFR 812.3(o) and ICH GCP E6 1.54). The term does not include any person other than an individual (i.e. it does not include a corporation or an agency).

- The obligations of a **Sponsor-Investigator** include both those of a sponsor and those of an investigator.
- If the PI is conducting an investigator-initiated study (i.e. federally funded grant submitted by the PI or a study funded through department or faculty start-up funds), he/she is considered the **Sponsor-Investigator**.
- If the Investigator holds the IND application with the FDA, he/she is considered a **Sponsor-Investigator** and must report directly to the FDA all protocol amendments, Information Amendments, Annual reports, and Serious Adverse Events (SAE).

Sub-Investigator

21 CFR 312.3(b) states: "In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 'Sub-investigator' (Sub-I) includes any other individual member of that team" but is primarily used to refer to other physicians for faculty colleagues that could be delegated tasks that require making critical study decisions.

Per ICH GCP [E6 1.54] A Sub-investigator is any individual member of the study team designated and supervised by the investigator at the study site to perform critical study-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). The sub-investigator should report directly to the investigator for his/her responsibilities related to the clinical research study (i.e., the investigator should have clear responsibility for evaluating the sub-investigator's performance and the authority to terminate the sub-investigator's involvement with the study).

A Sub-I assumes responsibility for tasks delegated by PI. The Sub-I must be as knowledgeable about the protocol and investigational product, as the PI because they may be delegated to conduct some or all aspects of the study including making critical study-related decisions.

Clinical Research Coordinator

The federal regulations clearly define the role and responsibilities of the PI and Sub-I, but not the Study Coordinator, also referred to a Clinical Research Coordinator (CRC). Nevertheless, it is clear that a CRC:

- *Works with and under the direction of the PI.*
  The clinical research coordinator is a specialized professional working with, and under the direction of the principal investigator.

- *Plays an integral role in day-to-day activities.*
  The investigator has ultimate responsibility for how a clinical trial is carried out, but the CRC plays an integral role in the day-to-day study activities and managing many logistical aspects of the study.

- *Can have very diverse roles and responsibilities.*
  The CRC's role and responsibilities can be very diverse. There may be a combination of administrative, financial, regulatory, and subject management responsibilities. It is important for the CRC to know the scope of their role and responsibilities.

- *Characteristically are organized, able to multi-task, and to give great attention to detail.*
  Some of the important qualities of a CRC are to be organized and to be able to handle multiple tasks simultaneously. Great attention to detail and strong time management skills are imperative. It is essential to keep accurate records, collect clean data, and keep participants safe.

- *May be licensed or unlicensed personnel.*
  Licensed personnel must work within their scope of practice. This includes licensed physicians, advanced practitioners (i.e. nurse practitioners, physician assistants) and licensed nurses, such as those with a Master's or Bachelor's degree in Nursing, or Registered Nurses (RN). Unlicensed personnel may not be delegated or perform tasks that they are not legally licensed or certified to perform.

Typical CRC Responsibilities

Successful CRC keep in mind that the PI is ultimately responsible for the conduct of the study, thus the study procedures must be conducted according to the PI's direction. Typical duties a CRC may perform include, but are not limited to:

- *Ensuring IRB approval is current*
  Even if the coordinator is working with the regulatory staff in their program, they should know IRB approval and expiration dates. The CRC should also ensure that all appropriate documents have IRB approval, and that only the most recently approved documents are used.

- *Obtaining informed consent*
  Any member of the study team may obtain informed consent from subject if they are qualified, have been properly trained on the informed consent process for the study and have been delegated this task by the PI. This process will be reviewed in more detail in a separate chapter later in the manual.

- *Protecting the rights, safety and welfare of subjects*
  Protecting the rights, safety, and welfare of study subjects is always important, and is the responsibility of all members of the research team.

- *Scheduling subject visits*
  When scheduling subject visits, the coordinator must often coordinate with many individuals, groups or other UW Health departments or clinics. This may include communication with other members of the study team to ensure their availability for the conduct of study procedures, and most important, they must work with the study subject. Depending on the subject population, individual subjects may need to coordinate study visits with their work schedules or to arrange child care. While coordinating all these

aspect may be difficult, study visits must still be scheduled within the visit windows defined in the protocol.

- *Completing all necessary study visit documentation.*
  Completion of study visit documentation may include activities prior to a study visit, for example, creating research orders in Health Link and documenting communication with the study subject. There is also documentation to be kept during the study visit. The documentation completed during a study visit could be as simple as documenting the time that procedures were performed. Or it could be more comprehensive, including documenting the subject's response to questions, updating their medical history or medications, and documenting adverse events. Documentation continues after the study visit. Depending on the type of study and the study sponsor, additional forms may need to be completed, such as Case Report Forms (CRF). The data may also need to be entered into an electronic data capture system or a study database.

- *Interviewing subjects/administering questionnaires*
  If appropriately trained, and delegated this task by the PI, the coordinator could conduct interviews and administer subject questionnaires.

- *Collecting and processing of biological samples*
  The coordinator may collect, handle, and process biological research samples or specimens, if appropriately trained, and delegated this task by the PI. The coordinator should also be aware of sample collection or processing procedures that may need to be performed by certified personnel.

- *Abstracting study data from the medical record*
  The coordinator may be asked to abstract data from the medical record to answer a specific research question or look for serious adverse events, such as emergency department or urgent care visits of actively-enrolled subjects.

- *Documenting and reporting adverse events*
  CRC should engage in a dialogue with the subject to explore adverse events, including all medical and non-medical related signs and symptoms the subject may be experiencing or have experienced since their last research visit.

The coordinator may report, or facilitate reporting of AEs or other Reportable Events to the appropriate regulatory authorities, such as the IRB, FDA, or Data and Safety Monitoring Board/Committee (DSMB/C). It may be the responsibility of the clinical research coordinator to report these issues to the IRB, or they may ask the regulatory specialist in their group for assistance. The PI must review all submissions, regardless of who submits reportable events to the IRB or other regulatory authorities.

- *Ensuring protocol compliance*
    - *By the study team* - The CRC should make sure all procedures defined in a protocol have been performed. It is appropriate for a CRC to review study specific data collection forms to ensure all data from each visit is captured.

    - *By subjects* - The coordinator should also determine subject adherence and compliance if defined in the protocol. If there are concerns, the coordinator should consult with both the PI and the subject to help determine if there are areas of improvement to focus on.

- *Maintaining Study and Subject Records*

The CRC should ensure that all study and subject records are maintained. There are additional chapters in this manual that describe study records and subject records in more detail.

- *Acting as an Advocate/Liaison/Communicator*

The CRC should always act as the subject's advocate. Sometimes this involves being a liaison to facilitate communication between clinical care staff, clinical research staff, the IRB, and the sponsor/CRO representatives.

- *Providing assistance to regulatory, recruitment, financial and data management staff.*

As mentioned earlier, the roles and responsibilities of a CRC can be very diverse and may depend on the specific study type, study sponsor, and research program. CRC may be asked to provide assistance to regulatory, recruitment, financial, and data management staff in their program, or they may be asked to perform all of these tasks.

Tasks a CRC Should Not Do

Unless the CRC is a licensed physician or advanced practitioner (i.e., PA or NP), a CRC is generally not qualified to:

- *Assess adverse events*

  While a CRC may identify the occurrence of adverse events, he or she is not qualified to assess the severity or clinical significance of such events. This is the responsibility of the PI or Clinical Investigator that has been delegated this task.

- *Perform Physical Exams*

  The coordinator should not perform physical exams. If a physical exam is required per the study protocol, the physical exam should be completed by a licensed physician or advanced practitioner.

- *Assess significant of abnormal laboratory values*

  A CRC may not review abnormal laboratory values to determine clinical significance. This task must be performed by a licensed physician or advanced practitioner.

- *Perform other tasks required of a licensed professional*

  There are some tasks that require a licensed professional, such as a blood draw from a central line, punch biopsies, lumbar punctures, etc. All members of the study team should be aware of their scope of practice and limitations.

- *Provide clinical care*

  If a licensed physician or advanced practitioner is also serving the role of a CRC, it is important to remember their role in the study is to conduct research, not to provide clinical care. Unless the CRC is also a member of a participant's clinical care team, they should not make any medical recommendations or answer non-study-related questions. The role of the CRC is to convey concerns about subject's medical conditions and non-study-related questions to a member of the subject's clinical care team.

Regulatory Staff

Like CRC, the federal regulations do not clearly define the role and responsibilities of a Regulatory Specialist. At UW-Madison, Regulatory staff are primarily responsible for the preparation, processing, and submission of applications and supporting regulatory documents, including consent forms, to the IRB and administrative or oversight boards and committees as applicable and according to regulatory and institutional requirements.

Regulatory staff is also expected to develop and maintain knowledge of federal and institutional guidelines, regulations, and requirements governing research. Regulatory staff is typically responsible for activities including, but not limited to:

- Preparing, processing and submitting initial IRB applications, change of protocol submissions, and continuing reviews to the IRB and other committees as applicable.
- Tracking study submissions, approvals and expiration dates to ensure uninterrupted project approvals.
- Processing IRB approval letters and accompanying approved documents, i.e., consent forms, recruitment material, subjects surveys/questionnaires.
- Ensuring all staff credentials (training, Curriculum Vitae (CVs), medical licensure, etc.) are current (not expired) and up to date.
- Preparing and maintaining the FDA 1572.
- Preparing and maintaining the regulatory files/binder.
- Communicating submission progress to the PI, the study team and the sponsor/CRO (as applicable).
- Preparing and submitting reportable events according to regulatory and institutional requirements.
- Preparing, processing and submitting final report to the IRB and other committees as applicable.

These are the typical tasks regulatory staff may be responsible for performing, but there are frequently additional duties that these staff perform or conduct, that may not be listed above.

Financial Staff

Financial staff plays a key role throughout the study. The financial staff member is integral to the budget development and negotiation process, identifying routine care versus research-related costs and the related financial impact on subjects, as well as routing the grant, contract, and/or agreement through UW-Madison as part of the study initiation process. Financial staff also play a role monitoring study account(s) throughout the course of the study to ensure all charges are appropriate and consistent with the grant/contract/agreement. Regularly occurring meetings with the PI and the study team is important, especially if there is a change to the protocol that could impact study costs. Financial management could be the responsibility of one member of the study team, or various financial-related tasks could be delegated to multiple members of the study team.

Recruitment Staff

Recruitment staff assist in the implementation of the recruitment plan to identify the target subject population, taking eligibility criteria into account. The recruitment staff is integral to identifying recruitment barriers and processes to overcome the barriers. Recruitment staff should identify all helpful institutional and local resources . Subject recruitment could be the responsibility of one member of the study team, or various recruitment tasks could be delegated to multiple members of the study team.

Data Management Staff

Data management personnel are responsible for the oversight of clinical research data. Data management tasks include data acquisition, data extraction, data entry, data processing/coding, continuous monitoring of timeliness and completeness of data entry, data security, and data quality. Data management could be the responsibility of one member of the study team, or various data management tasks could be delegated to multiple members of the study team.

Sponsor

The **sponsor** is the entity responsible for the initiation, management, and/or financing of a clinical research study. The sponsor does not actually conduct the investigation or administer/dispense the test article to research subjects (21 CFR 50.3(e), 21 CFR 312.3(b), ICH GCP E6 (1.53)).

The **sponsor** may be an individual, a pharmaceutical company, a governmental agency, an academic institution, a private organization, or another organization.

The **sponsor** may contract with a CRO to conduct some of the initiation and/or management activities that a sponsor is responsible for (i.e. monitoring).

UW Health Staff

UW Health staff may interact with research subjects as part of their clinical duties. For example, research subjects present in the clinical setting may be seen for medical and nursing care, collection of laboratory specimens, radiology tests, and other health-related interventions. UW Health staff should always communicate with the study team if there are any subject safety concerns or if they are unsure of research procedures to be conducted.

Nursing Staff

UW Health nursing staff caring for subjects participating in a clinical research study should follow UWHC policies unless instructed otherwise in the research protocol approved by the IRB of record. UWHC Policy 3.11 provides instruction on obtaining approval to conduct a study in the hospital or clinics. Nursing staff should be provided information by the study team on study protocol-required activities they will be required to conduct. Additionally, information on how to contact the study team should be provided to the clinical staff. This advance information is an essential part of preventing protocol deviations.

Non-UWHC Registered Nurses Working at UWHC

Registered nurses who practice at UWHC, but who are not employed by UWHC (i.e. employed through a SMPH Department), must obtain approval for practice at UWHC facility by the Education and Development for Nursing and Patient care Services and must be reapproved annually. Refer to UWHC Policy 4.37 for more information. Advanced practitioners, such as NPs and PAs who practice at UWHC must be approved for practice by UWMF, as applicable.

There is no approval to practice as a Licensed Practical Nurse or Medical Assistant at a UWHC facility. These staff members have the same limitations and restrictions as unlicensed personnel. Unlicensed personnel and the PI are responsible for knowing the scope of activities allowed for clinical research activities. Some restricted activities may be within the scope of practice for unlicensed personnel after obtaining approved training, such as phlebotomy training. Any uncertainties about approved activities should be clarified with the manager of the clinical department in which the study is being performed.

Study Pharmacist

Though the PI is ultimately responsible for drug accountability, UWHC policies require the Pharmaceutical Research Center (PRC), who employs a team of pharmacists and pharmacy technicians to perform the tasks of study drug storage, preparation, dispensation, and accountability (per UWHC policy 4.11). For more information about the PRC, refer to Chapter 11 describing the Clinical Research Resources.

D. Delegation of Authority Log

Throughout this module, duties are referenced that can be delegated to the members of the study team by the PI. These duties can be documented on the Delegation of Authority (DOA) log. This log may be the only record of the delegation of duties, and it is imperative to maintain this log.

Though there are many references to appropriate delegation of tasks to qualified staff, there is no federal regulation that explicitly references a **DOA Log.** Per the FDA Guidance on Investigator Responsibilities referenced above, the investigator should maintain a list of the appropriately qualified persons to whom significant research-related duties have been delegated. This list should also describe the delegated tasks, identify the training that qualifies such individuals to perform study related delegated tasks, e.g., can refer to an individual's CV on file, and identify the dates of involvement in the study. Obtaining the signatures of the staff involved in the conduct of the study allows future researchers to accurately reproduce the study activities. It is efficient to collect staff signatures on the same log that indicates the delegated duties and tasks. *An investigator should maintain separate lists for each separate study.*

Things to watch out for:

The start date for any staff member cannot be before he or she has 1) been listed on the approved IRB application; and 2) been trained. There should always be documentation of training with the topics and date of training. Some DOA logs will also require the PI to sign, or initial, and date when a study staff members starts. The date that corresponds to the PI's signature or initials should be the same as the start date.

Keep everyone on the team up to date and current

A key to conducting research responsibly is to make sure all study staff have the necessary resources and support to complete their delegated task(s). This could also include scheduling regularly occurring meetings to check in with other staff involved in the conduct or oversight of the study.

Regular and ongoing communication with members of the study team can help ensure that all involved:

- Have an adequate understanding of the specific details of the protocol needed to perform their assigned tasks.
- Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects.
- Are competent to perform delegated tasks.

- Are informed of any pertinent changes during the conduct of the study and receive additional training as appropriate.
- Understand the study purpose and how to assure data integrity.
- Are reminded of the study-specific inclusion and exclusion criteria.

E. Professionalism

Regardless of an individual's role on the clinical research team, it is important that those who interact with subjects remember that subjects are volunteering their time to participate, most often to benefit others in the future. They will also likely have varied backgrounds, beliefs, needs, and personalities. At any time, for any reason, a participant may withdraw from the study. Therefore, it is the job of all members of the research team to make participation a positive experience.

Always remember that participants come first.

- Establish rapport with participants. Retention begins with the first contact with the subject, is an ongoing process, and is everyone's responsibility
    - Treat participants, and their caregivers, with respect.
    - Assure a welcoming atmosphere where participants are seen.
    - Identify and resolve issues in a timely manner.
    - Additional considerations include:
        - Schedule appointments at locations that are convenient to the participant
        - Budget for items such as transportation reimbursement and ongoing participant contact, such as holiday and birthday cards
- Communication strategies
    - Contact subjects, or respond to communication from the subject, as soon as possible. The longer a subject waits before hearing back from study staff, the less confidence and trust they have in the study staff, and they may become more concerned or apprehensive.
    - Be persistent. Document all attempts to contact participants, and keep trying.
    - Obtain IRB approval for documents given to subjects.
        - Informational packets/folders that could include information sheets about their disease or condition, local support groups or services that may be available,
        - Tokens of appreciation to be given to research subjects i.e., special event cards, thank you notes)

- Correspondence including study visit reminders which could ask subjects to bring unused study drug to next appointment and to call if they experience any side effects or symptoms.

All research team members should do their best to minimize risk to research subjects

All research involves some level of risk. Investigators and members of the research team are obliged to give forethought to maximize the potential benefits and to minimize the potential risks arising from participation in the research study. We often think of risks in terms of physical harm that may occur as a result of participation in research procedures, but harm may also result from aspects of participation beyond research procedures. For example, harm may result from disclosure of findings from a research study.

According to the Belmont Report, Part C, Section 2, most risks encountered by participants in research fall into the following categories:

Physical:

Physical risks may include pain, injury, and impairment of a sense such as touch or sight. These risks may be brief or extended, temporary or permanent, and may occur during participation in the research or arise afterwards.

In many situations, physical risks in research can be minimized by carefully and skillfully following the protocol and by having trained individuals conduct research procedures, through careful monitoring of research participants' health status, by recruiting appropriate populations, and by providing clinical care when needed.

Psychological:

Psychological risks can include anxiety, sadness, regret, and emotional distress, among others. Psychological risks exist in many different types of research in addition to behavioral studies.

Possible ways to protect against psychological risks include reminding participants of their right to withdraw from research or limit their participation if they become uncomfortable, providing counseling or psychological support for participants who experience distress, or thoroughly debriefing research participants after research sessions are over.

Social:

Social risks exist whenever there is the possibility that participating in research or the revelation of data collected by investigators in the course of the research, if disclosed to individuals or entities outside of the research, could negatively impact others' perceptions of the participant.

Social risks can range from jeopardizing the individual's reputation and social standing, to placing the individual at-risk of political or social reprisals.

Often, minimizing social risks to participants involves protecting confidential data, including not only the data collected, but the fact of participation in the research project itself.

Legal:
Legal risks include the exposure of activities of a research subject "that could reasonably place the subjects at risk of criminal or civil liability."

Protections against legal risks often involve protecting the confidentiality of research data. For studies conducted in the United States, investigators can apply for Certificates of Confidentiality, which are intended to prevent investigators from being forced to disclose data that can be linked to identifiable research participants in legal proceedings.

Economic:
Economic risks may exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or to find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

Protecting confidentiality of data is one method for protecting against economic risks, such as those to employability and insurability. Investigators may elect to keep research data separate from medical records to prevent employers and insurance companies from obtaining information that could put the participants at risk.

F. Subject Responsibilities

The study subject is an integral member of the research team. Their role needs to be reinforced as part of the informed consent process. Responsibilities include:

- Adhering to the study visit schedule
- Complying with the study treatment
- Notifying the study team if there are changes in their medications or new conditions/diagnoses made during their study participation
- Keeping the study team up to date if there are changes in their home life such as a new job, a new address, a new phone number, etc.

G. Clinical Care vs. Clinical Research

According to the Belmont Report, the distinction between (clinical) research and (clinical) practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined." [taken from The Belmont Report: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html] Good clinical care of patients is not the same as GCP when working with research subjects. For the most part, the term clinical care refers to interventions that are designed solely to enhance the well-being of an individual patient with a reasonable expectation of success. By contrast, the term "research' describes an activity designed to test a hypothesis, permit conclusions to be drawn, and contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships)" [taken from The Belmont Report: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html] Often in clinical research studies, the investigator plays a dual role as physician and investigator. It is the duty of the physician and all members of the research team to act in the best interest of the participant, while at the same time performing good research. Differences in these roles must be understood.

Examples:

- Concomitant medications that might normally be prescribed for a patient may not be allowed for a subject while participating in a research study.
- Treatment periods, including run-in and wash-out periods, may differ from clinical practice.
- A symptom or side effect may be normal in certain disease states would be considered an adverse event during study participation.
- Unless authorized by appropriate licensure, members of the clinical research team should not give clinical research subjects health care recommendations.

Chapter 4: Protocol Content Essentials

A. What is a Protocol?

The protocol is a study plan, or an investigational plan, that describes how the clinical research study will be implemented. It should be written in a comprehensive manner to leave no room for misinterpretation.

A protocol is designed as an instruction manual on how to answer a specific research question, while protecting the rights, safety, and welfare of subjects. The protocol must include specific information about who may participate in the study, how many subjects will be studied, the primary measures to be evaluated, and the schedule of tests, procedures, medications, and dosages as applicable. The protocol should include the length of study participation, potential risks, and how adverse events will be handled. The protocol allows researchers at multiple locations (multi-site study) to perform the study in the same manner so that thei data can be combined as though as though all data was obtained at the same study site.

The protocol is at the center of any clinical trial. It details all the information required to safely conduct the study. A protocol may come from a sponsor, such as a drug company, or it may be developed by an individual investigator. Protocol formats can vary between companies and investigators, but the content should not. There are some sections in the protocol that may not be included, depending on the discipline being studied, as well as the phase of study. Not all study staff are involved in writing the protocol, but all members of the team should understand the necessary protocol components.

The contents of a clinical research protocol should generally include the following sections as described in this chapter. Site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

Additionally, the UW ICTR Clinical Research Toolkit includes a Protocol Checklist in the list of guidance documents and templates available online (https://ictr.wisc.edu/clinical-research-toolkit/).

Refer to the Clinical Trial Protocol development tools and templates created through an NIH and FDA collaboration: https://osp.od.nih.gov/clinical-research/clinical-trials/

B. Title Page

All protocols should have a title page. The title page will include the following information, as applicable:

- **Protocol Title.** The title should be specific enough to distinguish the protocol from those for similar studies. It should include the drug, disease being studied, design, and the study phase.
- **Protocol Number.** A unique number that identifies the protocol.
- **IND or IDE Number**, as applicable.
- **Protocol Date and Version Number.** All protocols should include a version number and version date that will allow subsequent versions to be identified.
- **Funding Sponsor.**
- **PI name and Institutional Affiliation.** The contact information for the study PI.
- **Sub-I(s).** Include name, department, address, phone number, FAX number and e-mail addresses for all protocol personnel.
- **Coordinating Center,** as applicable.

C. Table of Contents

Every protocol should include a Table of Contents to allow easy navigation.

D. Protocol Summary/Abstract

The protocol summary, or protocol abstract, should give a good overview of the study and usually includes the following:

- Study objectives/endpoints. A statement of the primary/secondary/safety/exploratory objectives and endpoints.
- Study population. A description of the population being studied, sometimes with inclusion/exclusion criteria.
- Study design. A statement that details what study design will be used.
- Study drug/device. The name (if known) and class, formulation, route of administration, and dosing regimen. Similar is true for an investigational device study. This section should include the device specification, the device manufacturer, as well as the device implantation or application.
- Duration of treatment, subject participation, and overall study projection.
- Methods and materials. A brief description of required procedures and tests.
- Anticipated maximum number of participants and study centers.
- A diagram or “schema” that represents the study design at a glance.
- The study schedule of assessments, also known as the protocol calendar.

E. Introduction/Background

The Introduction/Background section should identify the reason(s) for doing the study, any previous related studies, and how this study fits into the developmental plan. It should encompass the following:

- The name and description of the study drug/device, medical need, and rationale for use.
- A description of the design and major endpoints and rationale for use.
- A summary of findings from nonclinical and clinical studies relevant to the proposed study.
- A statement of how this protocol differs from other protocols using the same treatment.
- A description of the population to be studied.
- An identification of the setting in which participants will be seen.
- A summary of the known and potential risks and benefits, if any, to human subjects.
- A description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s) (investigational drug) or the device specifications and the device implantation or application should be described (investigational device).
- A description of the study control and/or comparison group.
- A general description of the procedures and length of the study.
- A statement that the study will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
    - Reference to earlier related studies and data regarding the investigational agent and disease or condition under study.
    - Discussion of implications for future studies.

F. Study Objectives/Aims

This section should clearly state the primary and secondary objectives and endpoints.

- State the primary objectives of the study (Purpose)
    - Example: Determine the efficacy of Agent A
- State the primary endpoints of the study (How the Objective is Measured)
    - Example: Determine if Agent A lowers blood pressure by a certain number or degree
- State the secondary, exploratory and or safety objectives and endpoints.

G. Study Design and Methods

The Study Design and Methods section provides specifics as to how the research will be conducted and the means used to achieve the study's specified objectives. This section may include the following:

- A description of the type/design of study to be conducted, e.g., double-blind, placebo-controlled, parallel design, and a schematic diagram of trial design, procedures, and stages.
- A description of the measures taken to minimize/avoid bias, such as randomization or blinding.
- A description of the treatment(s) and the investigational product(s) being tested.
- The expected duration of subject participation, and a description of the sequence and duration of all study periods, including any follow-up.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of the study, or the entire study.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of research treatment randomization codes and procedures for breaking codes.

H. Selection and Withdrawal of Subjects

This section should include a complete list and description of specific requirements for subject selection including age range, health status, disease specific criteria, allowable and disallowable medications, etc. Subject selection may be referred to as Eligibility Criteria or Inclusion/Exclusion Criteria in some protocols. The "eligibility criteria" details the inclusion and exclusion criteria for a subject to be eligible to participate. Inclusion criteria is the criteria that must be present for a subject to be eligible, whereas Exclusion criteria is the criteria that must NOT be present for the subject to be eligible.

These criteria should address:

- Willingness to sign an IRB-approved informed consent form and comply with the protocol requirements.
- Age, gender, and capacity.
- Disease or condition specific criteria.
- Required thresholds of physiologic and laboratory testing.
- Allowed and disallowed medications.
- Medical and surgical history.

- Ability to tolerate a withdrawal period from current treatment prior to study treatment (if applicable).
- Fertility limitations and restrictions for the duration of the study participation, both for participant and partner.
- A statement that the investigator can use judgment regarding any other condition not specified which may impact participation.
- Limit on concurrent participation in other interventional study.

This section should also include the subject withdrawal criteria, i.e., terminating investigational product treatment, and procedures specifying:

- When and how to withdraw subjects from the investigational product treatment.
- The type and timing of the data to be collected for withdrawn subjects.
- Whether and how subjects are to be replaced.
- The follow-up for subjects withdrawn from investigational product treatment.

I. Treatment/Intervention Plan

This section will include details of the treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment.

This section will give details about the investigational treatment(s) to be administered, including:

- Generic, chemical, and trade name
- Packaging
- Storage procedures and stability considerations
- Dosage form and formulations
- Formulation of placebo
- Dosing schedule(s)
- Treatment period(s), including follow-up period(s)
- Blinding procedures and code breaking process
- Dosage regimen, supporting rationale, and adjustment procedures (if necessary)
- Route/mode(s) of administration
- Compliance parameters.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during study participation.
- Procedures for monitoring subject compliance.

J. Investigational Product Details

This section includes specifics about the drug(s) being used and how they are stored and procured for use in the clinical trial. Industry-sponsored protocols may refer to a Pharmacy Manual for some detailed information. This section should include:

- Drug name (generic name) with IND number
- Classification
- Mode of action
- Storage and stability
- Dose specifics
- Preparation
- Route of administration
- Incompatibilities
- Availability
- Side effects
- Nursing implications

If the study is evaluating an Investigational Device, this section should instead include:

- Device specifications, packaging, labeling
- Device storage
- Device implantation/application
- Device accountability procedures
- Concomitant medications allowed/disallowed, required washout periods
- Use of sham procedures
- Precautionary, prohibited medications and procedures
- Prophylactic medications and procedures
- Device removal
- Clinical or laboratory evaluations required

K. Informed Consent

This section should include a statement that the informed consent requirements and regulations relating to informed consent will be followed, emphasizing the requirement for obtaining consent prior to performing any study-related activities.

L. Assessment of Efficacy

This section should include a detailed description of the efficacy measures to be recorded, including the identification of primary and secondary endpoints, and methods for recording and analyzing efficacy parameters.

Study endpoints are the variables chosen to assess the effects of the investigational product related to pharmacokinetic parameters, pharmacodynamic measures, efficacy, and safety.

- *A primary endpoint(s)* should reflect clinically relevant effects and is typically selected based on the principal objective of the study.
- *Secondary endpoints* assess other drug effects that may or may not be related to the primary endpoint. Endpoints and the plan for their analysis should be prospectively specified in the protocol.

The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

M. Assessment of Safety

This section will include the safety parameters that will be assessed, including the methods and timing for assessing, recording, and analyzing safety parameters. This may include procedures for eliciting and recording adverse events. The purpose of conducting ongoing safety assessments is to continually evaluate changes in subject risk or safety information over the course of the study.

Adverse Events

This section should include explicit descriptions and definitions of adverse events, as well as reporting requirements and the type and duration of the follow-up of subjects after adverse events. Refer to Chapter 9 of the manual for more information on the identification, documentation and reporting of adverse events.

N. Study Activities and Observations

Screening Procedures

This section will detail all the screening requirements that need to be addressed prior to enrolling subjects. These issues may include, but are not limited to:

- A description of all activities and tests needed prior to enrolling.

- Baseline values to be established at screening.

Replacement of Subjects

This section will describe the procedures to replace subjects who fail the screening, withdraw from the study, or whose participation is otherwise terminated.

Concomitant Medications

This section will address the use of other medications by subjects while enrolled in the study, over-the-counter and prescribed medications. This section should describe the medications that are allowed and those that are not allowed during study participation, including the procedures to be taken if a subject starts a disallowed medication during their participation in the study.

Subject Enrollment/Registration

This section will define the enrollment start for participants. Some studies consider the subject enrolled when informed consent is obtained, while others consider the subject enrolled when they are randomized or receive study treatment. Each study will clarify enrollment criteria.

Study Procedures

Study procedures section should include an outline of the laboratory and diagnostic tests required, as well as a study schedule for tests and procedures at each study visit throughout the study. Clinical assessments will also be described in this section.

Procedure	Screening - Visit 1	Baseline - Visit 2	Month 3 - Visit 3	Month 6 - Visit 4	End of Study - Visit 5
Informed Consent	X				
Medical History	X				
Physical Examination	X			X	
Venipuncture	X	X	X	X	X
Laboratory Tests [CBC, Comprehensive Metabolic Panel]	X	X	X	X	X
Eligibility Review	X				
Drug Dispensation/Accountability		X	X	X	
Questionnaires/Surveys		X	X	X	

O. Statistical Considerations

The study protocol should have a specified analysis plan appropriate for the objectives and design of the study.

This section is intended to address the study design, in relation to the objectives of the study and the plan for evaluation of the data.

- Overview of general study design issues
- Classification of study variables (primary vs. secondary)
- A description of the statistical models and methods to be employed, including timing of any planned interim analysis(es).
- The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each study site should be specified.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the study, including statistical and administrative procedures for monitoring the progress of the trial to implement early termination
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).
- Procedures for handling of non-evaluable or incomplete data

P. Direct Access to Source Data/Documentation

The protocol should include a statement that the investigator/institution will permit study-related monitoring, audits, and regulatory inspection by providing direct access to source documents and study data.

Q. Quality Control and Quality Assurance

The quality of a clinical research study is based on the study design and is embedded in the study protocol and procedures used to conduct the study. Components of the quality management procedures include:

- Creating, implementing, and upholding standard operating procedures (SOPs) (department, program, or study specific)

  The Quality Management section of the protocol describes the procedures that will be used during the study to protect data quality and integrity. Components of quality management procedures include creating, implementing, maintaining and following standard operating procedures, referred to as SOPs. SOPs could be implemented at the department level, the program level or for the specific study.
- A quality, well-designed protocol is integral to ensuring high quality data is collected and managed.
- Study team meetings and training. It's very important to have ongoing study team meetings to effectively monitor the progress of the study, and ensure the PI is providing appropriate oversight. The study team should pursue ongoing training offerings to keep abreast of the changing clinical research standards and regulations.
- The data must be collected, recorded and reported accurately. If it's not, the data may never meet the study objectives.
- Periodic monitoring and self-audits should be performed.

Additional information on how to protect data integrity will be discussed in Chapter 10 of this manual.

R. Adverse Events and Data & Safety Monitoring Plan

The Data and Safety Monitoring Plan (DSMP) describes the protections for research participants and data integrity, and the oversight for the clinical research study that will be provided, at a level commensurate with the study risks. Thus, the method and frequency of monitoring is directly related to the possible harms to research participants in the study. The Common Rule requires that all studies involving human subjects have a monitoring plan when appropriate (45 CFR 46.111). The NIH ofetn requires that all clinical trials supported by NIH have a DSMP: https://grants.nih.gov/grants/guide/notice-files/not98-084.html

NIH **Guidance for DSMP:**
Refer to the NIH Guidance on How to Write a Data and Safety Monitoring Plan: https://www.niams.nih.gov/grants-funding/conducting-clinical-trials/clinical-trial-policies-guidelines-and-templates/data-and

A Data and Safety Monitoring Plan should include the following elements:

- Description of how the progress of the study and the safety of subjects will be monitored
    - who will be monitoring and at what frequency
- Description of the mechanism for identifying and submitting reportable events to the IRB, FDA and NIH (as applicable)
    - How will problems/side effects be identified (lab tests, physical exams, etc.)
    - How will the problems/side effects be handled
    - What are the reporting requirements and timeframes
    - A detailed plan for stopping the study for safety reasons
- Plans for ensuring data accuracy and protocol compliance.

The processes used to monitor safety must be detailed and include specific descriptions of potential side effects and risks related to this specific investigation. Definitions and criteria for determining causal relationships to the investigation should be defined. This section of the protocol will vary depending on the type of study, and the levels of complexity and risk.

- For minimal risk studies, describe how potential problems will be monitored and handled, e.g., breaches of confidentiality, emotional upset
- For clinical studies or research involving more than minimal risk to subjects, describe:
    - Who will monitor subject safety and how often will events be assessed?
    - What follow-up procedures are required?
    - How will the events be recorded and communicated amongst research team members and who is responsible for submitting the reports?
    - The composition of the Data and Safety Monitoring Board/Committee (DSMB/C) if one has been formed for the study, and how frequently they will review the study
    - Describe stopping rules for the study
    - Describe what occurs if a subject withdraws prematurely

Data and Safety Monitoring Board/Committee

A DSMB/DSMC oversees and monitors on-going clinical research for safety and data quality issues. In addition to regular review of the data and safety measurements, they may review reports on QA, audits, monitoring and protocol deviations. They typically review all SAE reporting in real time via the DSMC Chair. Appropriate protections and oversight can range from

oversight by the PI and IRB for a single-site, minimal risk clinical trial, to oversight by a full DSMB and IRB(s) for a multi-site trial that involves greater than minimal risk.

Guidance documents available for researchers to refer to:

- OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: http://www.hhs.gov/ohrp/policy/advevntguid.html
- NIH Guidance Documents:
    - NIH Policy for Data and Safety Monitoring : http://grants.nih.gov/grants/guide/notice-files/not98-084.html
    - NIH Requirements for Data Safety and Monitoring Plans: http://www.nlm.nih.gov/ep/dsm.html
    - NIH: Further Guidance on Data and Safety Monitoring for Phase I and Phase II studies: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html
- FDA Guidance Documents: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
    - Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf
    - Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection, January 2009: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126572.pdf
    - Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, August 2013: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf
    - Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

S. Ethics

This section should include a description of ethical considerations related to the study. It may involve descriptions of independent ethics committees, reference to ICH principles, new information relevance and distribution, and subject confidentiality.

T. Data Handling and Record Keeping

This section will describe the data handling and record keeping processes and measures to be taken, including how data will be collected, protected, managed, and detailed procedures for correcting data. Data includes both study-related documentation supporting the conduct of the study, and subject-specific results of assessments which will be used for endpoint analysis. The descriptions should specifically state how, where, and under what secured conditions the data will be managed and maintained. Specific reference to hard copy and electronic information should be defined, including the use of electronic data capture systems, if applicable.

This section should also describe how long the study records will be kept. ICH, FDA, and

UW-Madison Human Research Protection program policies related to Data and Record Retention vary in terms of the length and determining time point for records retention.

U. Publication Policy

Publication policy, if not addressed in a separate agreement.

V. References

W. Supplements/Appendices

Chapter 5: Study Records: Management, Security and Retention

The discovery process for new diagnosis, treatment and prevention options can sometimes be perceived as burdensome and onerous, but every researcher must remember that none of these discoveries would be possible without valid data. Federal regulations, state laws, institutional policies, and good clinical and research practices require investigators to keep all study-related documents to effectively demonstrate that they follow the highest ethical and clinical research standards. While these regulations might seem overwhelming, it is important to understand that proper documentation not only provides the framework for appropriately organizing required paperwork, but also provides a tangible audit trail from the initial inception of the idea to completion of the study.

This chapter of the manual will be refer to research data**.** For the purposes of this manual, **Data** is defined as recorded factual material, regardless of the form or media on which it may be recorded, that is commonly accepted in the research community as necessary to validate research findings. This includes a variety of media and document types, such as data spreadsheets, films, sound recordings, or pictorial reproductions. Data is also used to describe records, such as the protocol, procedural manuals, data collection forms, SOPs, diagrams, and work flow charts that relate to the study.

Within this chapter, we will also describe the record keeping and retention regulations related to both the sponsor and the investigator. The sponsor of a study may be a pharmaceutical company, a non-profit organization or the UW-Madison PI. As a reminder, when the PI both initiates and conducts the clinical research study, the PI is considered the Sponsor-Investigator and assumes responsibilities of both the sponsor AND the investigator. If a study is industry-sponsored, it is important to know the regulations that apply to a sponsor, as well. Some sponsors, CROs, or federal agencies may require that investigators keep additional documents, and it is helpful to ask questions and understand why.

A. Federal Regulations for Record Keeping

US Federal Regulations discuss record keeping in several areas. Those areas differ depending on the type of study that is being conducted.

There are two sections that stand out in the CFR related to investigational drug records.
21 CFR 312.57 Record Keeping and Record Retention
21 CFR 312.52 Investigator Recordkeeping and Record Retention

There are additional 21 CFR 312 regulations relating to investigational drug accountability records, subject case history records, AE records, and the records that must be available for an inspector or auditor.

With regard to investigational drugs, 21 CFR 812.140 is more comprehensive and includes a section describing the records that must be maintained by the sponsor and the investigator. There is a separate section on the records that must be available for an inspector or auditor.

This chapter will describe the regulations relating to these records in more detail.

Information in the CFR can be found here: (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm).

B. International Conference on Harmonization Good Clinical Practice

The ICH GCP Guidelines related to recordkeeping are summarized below and can also be found on this website: ichgcp.net.

As discussed in Chapter 1: Basic Concepts of Clinical Research, the FDA accepted the ICH GCP guidance as standards to be followed when conducting an investigational drug or device study. It is also important to recognize that some sponsors, including federal agencies, require that the research they are funding follows GCP standards, even it if it not an investigational drug or device study. Therefore, it is expected that ALL types of clinical research studies will follow the GCP standards. A summary of ICH GCP guidelines related to record retention will be described in more detail below.

- Required records include all *original* records and *certified copies* of original records of clinical findings, observations, or other activities in a clinical research study necessary for the reconstruction and evaluation of the trial.
- Original documents may include: hospital records, clinical and office charts, laboratory notes, subject diaries, pharmacy dispensing records, and recorded data from automated instruments.
- Dates and signatures, or initials, should be legible. It should be clear who has documented the data (initial and date).
- The information should be documented in the correct time frame along with the flow of events. If a clinical observation cannot be documented when made, then the delay should be defined and justified.

- Data records should be easily accessible and available for review by treating physicians and during audits or inspections. The documents should be retrievable in reasonable time.

C. Protocol/Study Record Maintenance During the Conduct of the Study

Additionally, the ICH GCP guidelines refer to the necessary study records as **Essential Documents**. According to the ICH GCP Guidelines, **Essential Documents** are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the GCP standards and all applicable regulatory requirements.

Essential documents also serve a number of other important purposes. Filing essential documents at the study site or with the sponsor in a timely manner can greatly assist in the successful management of a study by the investigator, sponsor, and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of confirming the validity of the study conduct and the integrity of data collected.

A complete outline of the recommended documents can be found in the ICH GCP Website (ichgcp.net).

Additionally, the UW ICTR Clinical Research Toolkit provides Regulatory Binder guidance documents and templates (ictr.wisc.edu/CRToolkit).

D. Management of Study Records

The protocol records are stored in what is most commonly referred to as the **Regulatory Binder**. The term Regulatory Binder refers to the place where regulatory documentation related to the study is stored and updated. This place is not necessarily one location, or even one physical binder. It is also feasible to store some of the documents only in electronic format. If documents are only stored electronically, a paper placeholder should be stored in the regulatory binder that describes where the information is located and how to access it. It is important that whether study documents are electronic or paper records, they are always easily accessible to study staff, an inspector, an auditor, or a study monitor.

Regulatory Files/Binder should be created at the beginning of the study, prior to IRB approval and subject enrollment. As new documents are received, or as documents are revised or updated, the regulatory files must be kept current and up to date. Examples of documents that will likely have more than one version include the protocol, investigational drug brochure or investigators brochure, consent forms, and recruitment material. It is recommended to store documents in reverse chronological order, with the most current documents first. The Essential Documents must also be retained for a period of time after the study is concluded.

Below is a table containing the recommended Regulatory Binder sections and the applicable contents of each. This table provides an organizational framework and guidance on the documents that need to be maintained. Research teams are not required to follow the exact grouping or sequence of documents. Some of the sections or documents are not applicable to all studies. Additionally, investigators may choose to store certain documents in places other than the Regulatory Binder. Finally, some sponsors, CROs, or federal agencies may require that investigators keep additional documents that are not specifically referenced in this material.

Regulatory Binder Section	Regulatory Binder Contents	Applicable Guidance and Regulations
Study Team	● Study team contact list ● Form FDA 1572 *(If applicable)* ● Curricula vitae signed and dated for each member of the study team ● Copies of human subjects protection and HIPAA training certificates of completion for each members of the study team. ● Medical licenses *(if applicable)* ● Financial disclosure agreement(s) ● Conflict of interest management plans (if applicable) ● Signature log/delegation of authority log ● Protocol training documentation	*ICH GCP E6 2.7, 2.8, 3.1.2, 4.1.1, 4.1.5, 4.2.4, 5.18.4(b), 5.18.4(h), 8.2.10, 8.3.5, 8.3.24* *21 CFR 312.50, 312.53, 312.64(d), 312.57(b), 812.40, 812.43, 812.110(d), 812.140(b)(3)* *45 CFR 46.11, 164.530(b)(1)*

Regulatory Binder Section	Regulatory Binder Contents	Applicable Guidance and Regulations
Protocol	• Study protocol • Study protocol amendments (including protocol clarification letters) • Protocol or amendment signature pages • Case report form documents or data collection forms. • Manual of procedures/operations	*ICH GCP E6 1.44, 4.5.1, 5.11.1(c), 5.18.4(l), 8.2.2, 8.2.7, 8.3.2* *21 CFR 312.30, 312.53(3), 812.140(a)(1), 812.140(b)(1)*
Investigational Product *(as applicable)*	• Investigational drug brochure • Package insert/prescribing information • Investigator brochure • Device manual • Dispensation/accountability logs • Product receipt/packing invoices • Instructions for handling or use • Temperature logs • Master randomization list • Process/procedures for unblinding	*ICH GCP E6 1.10, 1.48, 2.4, 4.6.3, 4.7, 5.12.2, 5.13.1, 5.13.2, 5.13.4, 5.14.3, 5.18.4, 8.2.1, 8.2.11, 8.2.12, 8.2.14, 8.2.17, 8.3.1, 8.3.2, 8.3.6, 8.3.7, 8.3.8, 8.3.13, 8.3.23, 8.4.1, 8.4.6* *21 CFR 312.23, 312.40, 312.55, 312.57, 312.59, 312.60, 312.61, 312.62, 812.5, 812.110, 812.140*
Contracts/Grants and Budgets	• Confidentiality non-disclosure agreement • Clinical trial agreement or agreement with funding sponsor/agency(ies) • Finalized budget • Billing statements	*21 CFR 54.6*
Information given to subjects	• Approved informed consent document(s) and HIPAA authorization(s) *(current version may be kept in a plastic sleeve in the front of the section)* • Subject instructions, subject diaries, advertisements, recruitment material, etc.	*ICH GCP 3.1.2, 4.4.1, 4.8.1, 5.11.1(c), 8.2.2, 8.2.3, 8.2.7, 8.3.2, 8.3.3* *21 CFR 56.109* *45 CFR 46.109*

Regulatory Binder Section	Regulatory Binder Contents	Applicable Guidance and Regulations
IRB Approvals and Correspondence	• IRB submission and accompanying documents (protocol amendments, continuing reviews, revised consent forms) submitted for approval. • IRB approval/acknowledgement letters (initial review, change of protocol, continuing review submissions, and study closure) • IRB correspondence (IRB notification of reportable events, responses to reportable events. • Federalwide assurance letter • IRB roster or compliance statement	*ICH E2 III,* *ICH GCP E6 1.5, 1.45, 3.1.4, 3.3.6, 3.3.7, 3.3.8(d), 4.4.1, 4.4.3, 4.5.4, 4.10.1, 4.10.2, 4.11.1, 4.13, 5.11.1(c), 5.11.2, 5.11.3, 5.17.1, 5.17.2, 5.18.4(l), 5.18.4(o), 8.2.7, 8.2.8, 8.3.3, 8.4.7* *21 CFR 56.103, 56.109 (e&f), 312.53(c)(1)(vi)(a), 312.66, 812.35(a), 812.140(a)(1), 812.140, 812.150*
Food and Drug Administration (FDA)	• FDA form 1571 • IND/IDE submission (including letter of acknowledgment/approval and related FDA correspondence) • Safety and annual reports	*ICH GCP E6 5.10, 5.11.1(c), 5.17.1, 5.17.2,5.18.4(l), 8.2.9, 8.3.4, 8.4.7* *21 CFR 312.20(a), 312.23(11)(e), 312.30, 312.32,312.33, 312.40, 812.20*
Laboratory	• Lab certifications (CAP & CLIA) • Laboratory normal ranges • CV pathologist, if applicable • Specimen sampling, handling, labeling, storing, and shipping procedure(s)	*ICH GCP E6 8.2.11*
Study Tracking Logs	• Informed consent log • Subject log (screening, enrollment, withdrawal) • Log of protocol deviations, violations, or exceptions • Unanticipated problem log	*ICH GCP E6 4.3.4, 4.5.3,5.18.4(j), 8.3.20, 8.3.21, 8.3.22, 8.4.3*

Regulatory Binder Section	Regulatory Binder Contents	Applicable Guidance and Regulations
Monitoring/ Auditing	• Monitoring logs • Correspondence to/from study monitor • Monitoring reports (including site initiation and close-out) • Audit related correspondence (FDA, sponsor, third party)	*ICH GCP E6 5.18.4(q), 5.18.6, 8.2.19-20, 8.3.10-11, 8.4.5* *21 CFR 812.140(a)(1), 812.140(b)(1)*
Correspondence	• Study related correspondence between the site, sponsor, clinical research organization, etc. • Miscellaneous (case report form transmittal logs), etc. • Data and safety monitoring board/committee letters/reports • Study newsletters	*ICH GCP E6 8.3.18* *21 CFR 312.64(b), 812.140(a)(1), 812.140(b)(1)*
Serious Adverse Events	• Serious adverse events reporting form(s) and instructions • Investigational new drug safety letters • Completed serious adverse events reports (or note where they are located)	*ICH GCP E6 8.3.17, 4.11.1, 4.11.2, 5.17.1, 5.17.2, 5.18.4(o)* *21 CFR 312.32, 312.64(b), 812.46(b)*
Miscellaneous	• Equipment records (calibration/maintenance records to demonstrate that the equipment has been recently checked, calibrated, cleaned and maintained properly). • Clinicaltrials.gov and/or clinical trials reporting program registration • Other approvals (biosafety committee, clinical research unit, etc.) • Publications, presentations, manuscripts, etc.	*ICH GCP E6 5.18.4(b)*

E. Regulatory Files/Binder Tips To Remember

- Keep the Regulatory files/binder up to date. This may require setting aside time on a regular basis to review and update files and documents in the regulatory binder.
- Identify individual(s) responsible for creating and maintaining the regulatory files. Ensure that the individual(s) are aware of their responsibility.
- Store the records in a safe and secure location. Per ICH GCP E6 4.9.4, the investigator/institution must take measures to prevent accidental or premature destruction of these documents. This means that the study files should not be placed up against a wall in a hallway where they could be stolen or damaged. They should not be placed immediately under a sprinkler system to prevent accidental destruction of the records.
- Customize the regulatory files/binder to meet each study. The table above is a template; unused sections can be omitted and new sections added as needed.

F. Protocol/Study Record Storage after Protocol Completion/Study Closure

A study is completed when the data is considered final (no additional data needed, no more editing/analyzing of data needed). Study records can be archived after completion, but must be maintained for a specified amount of time. The investigator/institution should retain the study documents as specified in essential documents *[ICH GCP E6 8]* for at least 2 years *after the last approval of a marketing application* or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained [21 CFR 312.57, 21 CFR 812.140(d), ICH GCP E6 4.9.4].

To ensure UW-Madison complies with federal, state and institutional requirements for clinical research, the PI must ensure adequate records are retained and accessible for the required retention period to document study procedures and adherence with the IRB-approved application and protocol. UW-Madison's policy on Data Stewardship, Access and Retention (https://grad.wisc.edu/projectagreementsip/wp-content/uploads/sites/13/2013/09/datasteward.pdf) requires the maintenance of records for a minimum of 7 years after the study is discontinued or completed.

Research records should be maintained for the longest amount of time specified to meet the requirements, not the shortest. In the case of investigational drugs or devices, it often takes

much longer than seven years to reach marketing approval, thus the federal requirement for two years after marketing approval trumps the UW-Madison minimum seven year policy.
It is important to note, the record keeping requirements described in this manual relate to FDA regulated studies in the US. Studies conducted internationally have different regulations to be followed.

G. Record Keeping and Management Resources

Additionally, the UW-Madison Archives and Records Management Program has resources for the best practices for record keeping and research records that can be found here:

- Best Practices for Record Keeping: (http://archives.library.wisc.edu/records/trainmats/2012_12_Basic_University_Records%20-%20for%20hand%20out.pdf)
- Research Records: (http://archives.library.wisc.edu/records/trainmats/2013%20Research.pdf)
- Records Management toolkit: (http://archives.library.wisc.edu/records/resource.html#bulletins)

Chapter 6: Study Initiation Process at UW-Madison

Prior to initiating a study, the research team should be aware of the research setting in which they are conducting their research. The process below describes the study initiation process for clinical research studies within UW-Madison, but there may be additional requirements and steps to be taken depending on the research setting (i.e., community based, private medical practice, and research networks).

There are typically more activities that must be conducted for investigator-initiated studies, as some of the necessary documentation for steps described below are provided by industry sponsors.

The process of initiating a study at UW-Madison begins with the initial commitment to be involved in the study. This could be a grant submission, or signing a confidentiality agreement with an industry sponsor.

Activity	Investigator-Initiated	Industry-Sponsored
Feasibility Assessment Complete	Ensure the PI has the necessary resources and capabilities to carry out the proposed protocol, i.e., access to subject population, adequate time and resources.	In the event that an investigator is approached to conduct a study by an industry sponsor representative, there is often a sponsor feasibility checklist that must be completed prior to the study team's feasibility assessment.
Ensure study initiation documentation is complete	Ensure the grant/federal submission is complete and routed as appropriate.	Ensure the Confidentiality Disclosure Agreement has been routed for signature as appropriate.
Protocol Development/Review/ Consult with clinical research services that may be involved in the conduct of study procedures (www.ictr.wisc.edu)	Develop the protocol.	Review and become familiar with the protocol.
Become familiar with the investigational product	Review and become familiar with the investigational product. Submit appropriate applications (IND, IDE) to the FDA as appropriate.	Review and become familiar with the investigational product. Submit appropriate applications (IND, IDE) to the FDA as appropriate.
Budget Development	This would have likely occurred during the grant submission process.	Budget Development and review by applicable Ancillary Services that may be involved in the conduct study procedures.
Reach out to Ancillary Services that may be involved in the conduct of study procedures	Initiate communication with groups such as CRU, PRC, etc. (reference above section).	Initiate communication with groups such as CRU, PRC, etc. (reference above section).
Budget Negotiation	This would have likely occurred during the grant submission process.	Budget Negotiation with the sponsor or CRO.
Route Contract/Agreement through RSP	Ensure the grant/federal funding related documentation is complete and routed as appropriate.	Ensure the Clinical Trial Agreement (CTA), or contract, has routed for signature as appropriate.

Activity	Investigator-Initiated	Industry-Sponsored
Draft the Informed Consent Document	Refer to the UW-Madison Health Sciences IRB Guidance and Informed Consent Wizard (include link).	Work with the industry or CRO representative to include the necessary sponsor and IRB standard language.
Develop study data collection forms (visit/procedure checklists, worksheets, source documents, CRFs, etc.)	Develop (or review one provided by a network) the study data collection forms to collect the necessary data in a consistent and analyzable manner (available networks, OnCore CRFs).	Typically provided by industry sponsor or CRO.
Develop an Instruction Manual or Manual of Procedures	Develop (or review one provided from by a network) a manual to describe how to conduct all study procedures and complete the corresponding documentation (available templates?).	Typically provided by industry sponsor or CRO.
Develop study database	Develop (or train on one developed by a network) a database or an electronic data capture mechanism to consistently collect, maintain, and securely store study data (OnCore or REDCap).	Typically provided by industry sponsor or CRO.
Prepare Recruitment Materials (must be included in the IRB Initial Application submission)	Develop a recruitment plan that is appropriate for your subject population, and prepare recruitment materials.	Develop a recruitment plan that is appropriate for your subject population, and prepare recruitment materials.
IRB Initial Application Submission *(after other applicable committee approvals, i.e. Biosafety Committee, Radioactive Drug Safety Committee, etc.)*	Submit the Initial IRB application (typically HS-IRB) using the electronic IRB software system (ARROW). Studies that will be routed to a central IRB, i.e., CIRB, WIRB, must first be submitted using the UW-Madison process.	Submit the Initial IRB application (typically HS-IRB) using the electronic IRB software system (ARROW). Studies that will be routed to a central IRB, i.e., CIRB, WIRB, must first be submitted using the UW-Madison process.

Activity	Investigator-Initiated	Industry-Sponsored
Initiate the ClinicalTrials.gov registration as applicable	All necessary information must be completed by the Responsible Party, which may be the PI if the study is investigator initiated.	Typically, the industry sponsor is the Responsible Party.
Create the Regulatory Binder (including essential documents such as the DOA/Signature log, Training log, contact list, etc.)	Develop the essential documents and create the Regulatory Files/Binder to organize the documentation currently available, designating sections for future documentation (templates).	Develop the essential documents and create the Regulatory Files/Binder to organize the documentation currently available, designating sections for future documentation (templates).
Confirm all procedures are in place for specimen/sample handling	Create a laboratory manual and corresponding documentation related to specimen/sample handling (templates).	Typically provided by industry sponsors.
Document IRB Approval	Include a copy of the IRB approval letter in your regulatory files (paper), upload to the OnCore system, and enter the review in OnCore (PC Console > Reviews > IRB).	Include a copy of the IRB approval letter in your regulatory files (paper), upload to the OnCore system, and enter the review in OnCore (PC Console > Reviews > IRB).
Finalize the ClinicalTrials.gov registration as applicable	All necessary information must be completed by the Responsible Party, which may be the PI if the study is investigator initiated.	Typically, the industry sponsor is the Responsible Party.
Obtain study account number	Request and obtain study account number and secure internal requisitions and/or external work orders.	Request and obtain study account number and secure internal requisitions and/or external work orders.
SMPH Review	Initiate the SMPH Review process to ensure the study is ready for UWHealth Study Registration (link to KB).	Initiate the SMPH Review process to ensure the study is ready for UWHealth Study Registration (link to KB).

Activity	Investigator-Initiated	Industry-Sponsored
Site Initiation Visit	Conduct a team meeting to review the protocol and related procedural details.	This is typically conducted by the industry sponsor/CRO.
Open study to accrual	Complete necessary steps to open the study to accrual. This may be done using the OnCore clinical trial management software.	Complete necessary steps to Open the study to Accrual. This may be done using the OnCore clinical trial management software.
Subject Recruitment/Enrollment	After the study is open to accrual, the study is ready to begin recruiting and enrolling subjects.	After the study is open to accrual, the study is ready to begin recruiting and enrolling subjects.

Chapter 7: Informed Consent Process

Much of the information presented in this chapter was taken directly from the DRAFT Guidance for IRBs, Clinical Investigators and Sponsors: Informed Consent Information Sheet (http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm)
And the Office for Human Research Protections (OHRP) Tips on Informed Consent: http://www.hhs.gov/ohrp/policy/ictips.html

A. What is Informed Consent?

Informed consent is one of the primary ethical considerations in research involving human subjects. The Belmont Report: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* describes the purpose of informed consent as the mechanism to ensure that participants understand the research study and voluntarily agree to participate. A copy of the Belmont Report may be found at the following site: (http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html).

Informed consent is more than just a form, and more than a signature on a form, it is a process of information exchange designed to:

1) provide the subject with all the information that he/she would reasonable want about a study to make an informed choice;
2) ensure that the subject understands the information presented;
3) discuss the individual's rights as a research subject; and
4) give the subject an opportunity to ask question and volunteer to participate in the study.

The informed consent process is one of the key mechanisms for ensuring that the rights, welfare, and safety of research subjects is protected. Just like protecting the rights, welfare and safety of human subjects is a continuous process, informed consent is an ongoing process and is not intended to be a one-time occurrence, but rather an ongoing process throughout the conduct of the study.

The informed consent process is the application of one of the principles of the Belmont Report, *Respect for Persons*. According to the Belmont Report, "Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied."

The Belmont Report, *Part C. Applications*, outlines three fundamental aspects of the informed consent process:

Information

- The Informed consent document is intended to include information necessary to inform research subjects about the purpose, risks, potential benefits, and alternatives to the research. This information should allow people to make a decision about whether or not to participate based on their own goals and values. The exchange of such information during informed consent should occur both at enrollment and throughout the study. Refer to the *8 Elements of Informed Consent* (45 CFR 46.116(a)) for more information.
- The information must be provided in such a way that it provides a reasonable person the information she or he would need in order to make an informed decision.

Comprehension

- Investigators are responsible for providing information during the informed consent process in a manner that can be comprehended by potential participants. Additional procedures may need to be in place for subject who do not fluently speak English or have a low literacy level.
- Investigators should not enroll anyone in a study unless the investigator is confident that the individual comprehends all information disclosed and agrees to procedures described during the informed consent process.

Voluntariness

- Potential participants must understand that enrolling in the research is voluntary and that they may withdraw from the study at any time without penalty or loss of benefits (45 CFR 46.116(a)).
- Individuals' decisions about participation in research should not be influenced by anyone involved in conducting the research: "...consent must be freely given or truly voluntary." [Respect for Persons, p 3 *Informed Consent*. Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.189.]
- For participation in research to be voluntary, there must be no coercion and undue influence.

B. Who Should Conduct the Informed Consent Process?

The PI is legally responsible and ethically obligated to ensure an adequate informed consent process and written informed consent is obtained from each research subject before participating in the research study, even when delegating the task. The intent of the regulations is to ensure that the person best equipped to answer the prospective subject's questions is present during the consent discussion. Typically, this means the PI, however, the PI may delegate this task to another member of the study team depending on the complexity of the study, urgency of the medical condition, and involvement of vulnerable populations. These are questions that are important to consider when developing and submitting the protocol to the IRB for review. It may not be necessary for the PI to personally conduct the entire consent process, but if the study involves medical treatment, a clinical Investigator must be available to answer medical, medication, or device questions that are most appropriately answer by a physician.

IRBs, PIs, and research sponsors all share responsibility for determining if the informed consent process is appropriate. The IRB application includes a description of the planned consent process as well as who the PI has delegated to conduct the informed consent process. This includes information such as the timing of obtaining informed consent and of any potential waiting period between informing the subject and obtaining the consent. The PI is responsible for ensuring informed consent is obtained in an adequate manner. It is critical that the research team member obtaining informed consent has been appropriately trained and the task has been delegated to them by the PI. This should be documented on the training log and DOA log.

Prior to approaching subjects to discuss their participation in a research study.

- Make certain to know the protocol. Review the study parameters and the study schedule so questions can be answered easily.
- Make certain to review the consent form before presenting it to a subject so that it is presented to the subject in a way that conveys a clear understanding of the study.
- Select an appropriate location. Respect the privacy of the potential participant by choosing a setting that is not open to the public. There should always be time set aside so a private, confidential, and safe setting is afforded to facilitate a constructive dialogue between the prospective subject and the person(s) involved in obtaining informed consent. A physician's office, a consultation room, or a clinic exam room would be examples of appropriate locations to meet with the subject. A patient waiting room, a

cafeteria, or pre-operative area would be examples of locations that may not be conducive to conducting the informed consent process.

- Ensure enough time has been set aside to review the study and the consent form in detail.
    - How much time is provided and/or available before study procedures are conducted? Approaching prospective subjects on the same day as the procedure needs to take place may not be sufficient. Participants may need time to think about their decision or to discuss their involvement with family, friends, primary care physicians, social workers, clergy, a patient representative, or other trusted advisors.
    - Discussions with prospective participants should take place with sufficient time for them to consider participation. It can be very difficult to absorb study details in one sitting, especially at a time of emotional distress. Subjects should be given the option of taking a copy of the document home so they can review it in their own time to consider participation.
    - For best results, participants should be approached when they are willing to listen, and are open and ready to consider consenting.

C. How Should Informed Consent be Obtained?

It is important to distinguish between the informed consent document and the informed consent process. While the informed consent document itself is important and is required to contain specific elements and language, “the procedures used in obtaining informed consent should be designed to educate the subject population in terms that they can understand” (OHRP Tips on Informed Consent). Think of the document as a teaching tool that can be used to guide the informed consent process, reviewing each of the required elements in the document.

Clinical research coordinators should act as advocates for study participants and ensure that all subjects fully understand the study. This involves more than a brief overview of what the study will involve. When speaking to participants, remind them that the consent form contains all the information under discussion and can serve as a reference whenever needed. During the consenting process, each of the required elements of informed consent should be discussed with the subject.

The required elements of Informed Consent are described below.

- Explain that the study involves research.
- Describe the purpose of the research study.
- Describe the duration of the subject's participation.
- Explain the procedures to be followed.
    - Review specifics of what participation will involve. DO NOT underestimate the time commitment.
    - Describe:
        - Number of visits.
        - Tests that will be performed, including blood draws and laboratory tests (including any fasting blood draws).
        - Time commitments. It may be helpful to provide a schedule of visits.
        - Data that will be collected from procedures that will be done as part of the subject's routine clinical care.
    - If reimbursement for time or travel is provided, it must not be coercive in amount or method of distribution. The consent form must describe the reimbursement mount and the methods and requirements for receiving (i.e., compensation for each visit completed OR mileage reimbursement to and from the subject's home to the research clinic).
        - If compensation is provided to minor subjects, describe who the compensation will be provided to (i.e., XXX provided to the child and XXX amount provided to the parents for each visit).
- Identify any procedures that could be considered experimental.
- Explain any reasonably foreseeable risks or discomforts to the subject.
    - Inform the subjects of the reasonably foreseeable harms, discomforts, inconvenience and risks that are associated with the research activity.
        - Use understandable AE terminology or definitions for technical terms.
        - Explain the implications of AEs that may not be familiar.
        - Convey the likelihood of side effects. Terms such as "likely," or "uncommon" aren't helpful by themselves.
        - Describe any treatments or procedures that may involve risks to the subject (or to the embryo or fetus) if the subject is or may become pregnant). If it is unknown, this should also be described.

        - The subject should also be made aware if there may be unforeseeable risks associated with study participation.
- Describe any benefits to the subject or to others which may reasonably be expected from the research. If the subject may not experience direct benefit, but rather the only benefit may be helping the public at large, this should be disclosed.
- Disclose all appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. This may include a description of the standard, routine clinical care procedures and approved medications are already available.
- Describe how the confidentiality of records identifying the subject will be maintained.
    - The OHRP Tips for Informed Consent recommends describing those who will receive the results of the research, including if subjects will receive the results of any research procedures. The regulations insist that the subjects be told of the extent to which their personally identifiable private information will be held in confidence. For example, some studies require disclosure of information to other parties.
    - Some studies inherently are in need of an NIH Certificate of Confidentiality (http://grants.nih.gov/grants/policy/coc/index.htm) which protects the investigator from involuntary release, i.e., subpoena, of the names or other identifying characteristics of research subjects.
- Describe the compensation available if research related injury (i.e., physical, psychological, social, financial, or otherwise) occurs and whether any medical treatments are available, what they consist of, and where additional information may be obtained.
    - Refer to the Health Sciences IRB website describing the UW Compensation for Research-related Injury language for more information: https://kb.wisc.edu/hsirbs/page.php?id=18647
- Describe, and show the subjects where in the consent form they can find contact information if they have questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
    - According to the OHRP Tips in Informed Consent, the regulations require the identification of contact persons who would be knowledgeable to answer questions of subjects about the research, rights as a research subject, and research-related injuries. These three areas must be explicitly stated and addressed in the consent process and documentation.

  - A single person is not likely to be appropriate to answer questions in all areas. Questions about the research study and related procedures may be best answered by the investigator(s). However, questions about the rights of research subjects or research-related injuries (where applicable) may best be referred to those not on the research team. At UW-Madison, these questions should be referred to UWHC Patient Relations Representative at 608-263-8009 or the University of Wisconsin Medical Foundation Patient Relations Representative at 800-552-4255 or 608-821-4819

- Clearly explain that participation is voluntary. It must be made clear to subjects that they can choose not to participate or choose to participate and later withdraw at any time without penalty or loss of benefits to which the subject is otherwise entitled.
  - Taken from the Consent Form Templates that can be found on the Health Sciences IRB office, UW-Madison standard language is “Your decision to participate in this research is entirely voluntary. You may choose not to participate. If you do decide to participate, you may change your mind at any time without penalty or loss of benefits that you had prior to the study. You will be told of any new and significant findings which may affect your willingness to continue. Your decision of whether or not to participate in this study will not affect the quality of your medical care at this institution.”
  - If there are procedures that must be conducted if a subject chooses to withdraw, these should also be discussed.
- Explain any anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent must be explained.
- Describe any additional costs to the subject that may result from participation in the research.
  - Review who will cover the costs of the research study procedures. If data will be collected from procedures that will be done as part of the subject’s routine clinical care, explain that the subject or the subject’s insurance will be responsible for payment.
  - DO NOT make promises to subjects that cannot be upheld, e.g., statements that the study will pay for the procedures if the subject can’t afford them.
- Describe how new information identified during the study, that may impact the subject's willingness to continue participation, will be provided to the subject.

    - According to the OHRP Tips for Informed Consent, the study team should let the subject know that if additional risks are identified during the course of the research, the consent process and documentation may require revisions to inform subjects as they are re-contacted or newly contacted.
- Include the approximate number of subjects involved in the study.

HIPAA Authorization Form

In addition to the informed consent document, there are elements in the Health Information Portability and Accountability Act (HIPAA) authorization form that must be reviewed with the subject. The HIPAA Privacy Rule defines how health care providers, staff, trainees and students in clinical training programs can use, disclose, and maintain identifiable patient information, called Protected Health Information (PHI). The health information privacy requirements went into effect for the use of PHI for research on April 14, 2003, requiring researchers to obtain written authorization from research participants before using or disclosing participant PHI for research purposes.

PHI is health information or health care payment information that identifies, or can be used to identify, an individual patient. The privacy rule very broadly defines identifiers to include, not only patient name, address, and social security number, but also fax numbers, email addresses, vehicle identifiers, URLs, photographs, and voices or images on tape or electronic media. When in doubt, assume that any individual health information is protected under the privacy rule.

In some cases, the HIPAA elements are embedded in the informed consent document, making it a combined informed consent/HIPAA authorization form. In other cases, the HIPAA authorization form is a separate document. Regardless, HIPAA elements must also be discussed with the potential subjects. Describe**:**

- How the subject's health information be used for research
- What information will be used for research
- Who will use the subject's health information for research
- How long the subject's permission will last
- That the subject's permission is voluntary
- How health information will be protected

For more information, visit the UW-Madison HIPAA website: http://www.hipaa.wisc.edu/

Prior to Signing the Informed Consent/HIPAA Authorization Form

After the potential subject has had ample time to review the consent form and ask questions, assess the subject's comprehension about the material presented, including the nature of the study and voluntary participation. This can be done during the informed consent discussions, at the end of the process or both. This assessment may be done by asking open ended questions that begin with words such as "what," "where," "how often," "when," and "please describe." Subjects should not be asked closed-ended questions that allow simple "Yes" or "No" answers.

A few potential questions include:

- Please describe in your own words the purpose of the study. NOT: Do you understand the purpose of this study?
- What more would you like to know? NOT: Do you need any more information?
- What are your concerns? NOT: Do you have any concerns?
- Please explain to me what we're going to ask you to do.
- What are the risks you may experience?
- What are your concerns?
- What more would you like to know?

Such assessment allows the person obtaining informed consent to get direct feedback about what the subject recalls from the consent process and what information may need to be reviewed. An informed consent assessment is not meant to be a pass/fail quiz, but a tool for identifying gaps in the person's understanding of the study and what areas may require more discussion. If the subject doesn't seem to understand key points after repeated discussion, there may be other concerns and potential reasons to not enroll the subject.

To help subjects understand the information presented and so they have something to easily refer back to later, they may be provided with additional IRB-approved educational materials such as brochures about research in general and/or about the specific procedures used in the study for later reference.

Signing the Informed Consent/HIPAA Authorization Form

When all of the subject's questions have been answered and they have adequate information to make an informed decision to participate in the study:

- The subject, LAR (if applicable), and person obtaining consent must sign and date each consent form if there is more than one. Note: the federal regulations do not explicitly require a signature/date of the person obtaining informed consent. However, a signature/date of the person obtaining informed consent is considered best practice and expected per ICH GCP.
- The subject must also sign and date the HIPAA authorization form, if the HIPAA authorization form is a separate document and not combined with the consent form
- The subject must receive a copy of the consent and HIPAA Authorization form(s). FDA regulations do not require the subject's copy to be a signed copy, although a photocopy with signature(s) is preferred so there is never any concern about which version was signed.
- The research team must verify that there have been no alterations to the consent form document itself before it is signed.

Use of a Short Form and Study Summary

The informed consent documentation requirements [21 CFR 50.27] permit the use of either a written consent document that embodies the elements of informed consent or a short form stating that the elements of informed consent have been presented orally to the subject. When this method is used, there should be a witness to the oral presentation. Also, the IRB must approve a written summary of what is to be said to the subject or the representative. Only the short form itself is signed by the subject or the representative. However, the witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary. A copy of the summary is given to the subject or the representative in addition to a copy of the short form.

Documentation of Informed Consent/HIPAA Authorization

A signature on an informed consent/HIPAA authorization form alone is not considered sufficient documentation to demonstrate that subjects were given enough time to consider participation, received answers to any questions they might have, and were given a copy of the informed consent document. The informed consent process **must** be documented. This could be done in the research chart, e.g., in a progress note in the research chart using an informed consent

process source document, a study visit note, and/or in the HealthLink electronic medical record. If consent is obtained the same day that the subject's involvement in the study begins, it is essential to document the time that the consent was obtained to ensure that study specific procedures were performed only after obtaining the consent of the subject.

Storage of the Signed Informed Consent/HIPAA Authorization Form Documents

The original signed consent document must be retained in the study records. The original signed consent forms can be kept in the subject's research chart or in a binder intended solely for storage of original signed consent documents.

D. Ongoing Process

Obtaining informed consent is an ongoing process. Study staff should consult regularly with subjects throughout their participation in the study to ask if they have any questions and if they wish to continue participation.

E. Challenges with the Informed Consent Process

Language

Additional considerations come into play when recruiting subjects who are illiterate, have limited reading skills, or do not fluently speak English. This may mean adjusting the reading levels of documents provided or translating documents and presentations into the language with which participants are most comfortable.

Depending on the type of informed consent document used, i.e., Short Form, there may be additional requirements, such as a signature of a witness.

Non-English Speaking Subjects

Non-English speaking subjects must be provided with an IRB approved consent document translated into their language and the informed consent process must also be delivered in a language that is understandable to the subject. (45 CFR 46.116). The informed consent process may require a translator to interpret for the person obtaining informed consent including translating any questions the subject may have and their answers. While a translator may be helpful in facilitating conversation with a non-English speaking subject, oral translation of the consent document should not be substituted for a written translation. When the study subject

population includes non-English speaking people or the clinical investigator or the IRB anticipates that the consent interviews will be conducted in a language other than English, the IRB will require preparation of a translated consent document and assurance as to the accuracy of the translation. Non-English speaking subjects must also receive a copy of the informed consent document in a language they can understand.

If a non-English speaking subject is encountered unexpectedly, investigators will not have a written translation of the consent document and must rely on oral translation. Investigators should carefully consider the ethical/legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented, the subject's consent will not truly be informed and may not be legally effective.

Illiterate English-Speaking Subjects

A person who speaks and understands English, but does not read and write, can be enrolled in a study by "making their mark" on the consent document, when allowed by applicable state law.

A person who can understand and comprehend spoken English, but is physically unable to talk or write, can be entered into a study if they are competent and able to indicate approval or disapproval by other means. If (1) the person retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained verbally (still competent) and (2) is able to indicate approval or disapproval to study entry, they may be entered into the study. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire consent process and sign the consent document. A video tape recording of the consent interview is recommended.

Refer to the HSIRB website for guidance on the consent process for Non-English or Limited English speaking research participants: https://kb.wisc.edu/hsirbs/page.php?id=22202

Subjects with Diminished Autonomy

An individual’s autonomy can be affected by several factors including age, cognitive impairment, illness, and treatments. An individual’s capacity to consent to a particular study should be assessed based on:

- The individual’s level of capacity,

- The complexity and risks of the study, i.e., the capacity needed for an individual to be able to understand the study well enough to consent to participate, and
- The Belmont principle of respect for persons states that investigators need to make special provisions when including individuals in research who have diminished capacity for making decisions in their own best interests.

Therefore, DHHS regulations require that an Legally Authorized Representative (LAR) provide voluntary informed consent for individuals with diminished capacity to participate in research (45 CFR 46.116).

While DHHS regulations allow for LAR to make substituted decisions for individuals who need assistance, investigators should obtain consent from the participants to the extent possible. Some individuals may be only temporarily or intermittently incapacitated, e.g., due to injury or medications. In these situations, investigators should attempt to approach these individuals at a time when they do have the capacity to consent to research. If a participant regains the capacity to consent to research after the research has begun, investigators should obtain the participant's informed consent before continuing his or her participation in the study.

The individuals below are in order of priority for consent purposes under Wisconsin law. Consult them in the order they appear.

Subject with Capacity. If a potential subjects has capacity to consent to the research, informed consent must be obtained from him or her. If the subject with capacity has an activated research or healthcare power of attorney or a court-appointed guardian, please contact the UW-Madison Office of Legal Affairs at 608-263-7400. Capacity to consent is presumed to exist unless there is evidence to the contrary.

Subject with Variable Capacity. A potential subject who has variable capacity may consent during a period of capacity. When the lack of capacity is temporary and likely to end in a short period of time, the investigator should wait, if possible, until the subject regains capacity to seek consent for research participation.

Subject with a Research Power of Attorney. A research agent may consent to a potential subject's participation in research to the extent that the agent's decision is consistent with the wishes and preferences of the potential subject as expressed in the power of attorney instrument.

Subject with a Guardian. A court-appointed guardian of the person, but not a guardian of the estate or guardian ad litem, may consent to a ward's research participation. Under Wisconsin law, a guardian of the person may consent to research on behalf of the ward, if the research is minimal risk or the research holds out the prospect of direct benefit to the ward. The guardian of the person may consent to research on behalf of the ward that is more than minimal risk with no prospect of direct benefit only if the guardian can show by clear and convincing evidence that the ward would have elected to participate in such research.

Subject with a Power of Attorney for Healthcare Decisions. A healthcare agent designated in a power of attorney for healthcare may consent to a potential subject's participation in research to the extent that the agent's decision is consistent with the wishes and preferences of the potential subject as expressed in the power of attorney for health care instrument. Under Wisconsin law, a healthcare power of attorney is activated when two physicians or one physician and one licensed psychologist determine that the subject lacks capacity. Such determination must be documented in writing.

Subject with no Research Power of Attorney, no Guardian, and no Healthcare Power of Attorney. If the potential subject is found to lack capacity, then the potential subject's next of kin may consent on behalf of the potential subject. Any next of kin representative of the potential subject should be actively involved in the care of the subject. In the following order of priority, next of kin includes: the spouse, adult child, parent, adult sibling, grandparent, adult grandchild, or a close friend of the potential subject.

The UW-Madison IRB must approve the inclusion of subjects with diminished capacity to provide informed consent. This subject population cannot be enrolled unless the study is approved to do so.

The HSIRB website contains guidance when working with subjects with impaired decision-making capacity on the website dedicated to Special Consent Processes: https://kb.wisc.edu/hsirbs/page.php?id=18662

Pregnant Women in Research

Additional considerations should be given when the study is enrolling pregnant women or women who become pregnant during the course of the study.

Because research involving pregnant women may affect the woman, the fetus, or both the woman and the fetus, additional issues must be considered for studies of pregnant women.

The DHHS regulations require:

- Preclinical studies be completed prior to the involvement of pregnant women
- Consideration of risks and potential benefits for the fetus and pregnant woman

The DHHS regulations prohibit:

- Inducements of any kind to terminate a pregnancy
- Investigators from taking part in decisions about terminating a pregnancy
- Investigators from determining the viability of a neonate

Investigators, IRBs, and funding agencies must comply with requirements described in Subpart B of the DHHS regulations.

Children Participating in Research

Children may not have full capacity to make decisions in their own best interests; and therefore:

- Children are considered a vulnerable population, and
- Children are unable to provide “legally effective informed consent” as required by the HHS regulations at 45 CFR 46.116

Because children cannot provide informed consent, children provide assent to participate in research, to the extent that they are able, and parents/guardians give permission for a child to participate in research.

The additional regulatory requirements of assent and permission for research involving children (45 CFR 46.408) are intended to ensure investigators respect the decisions of both children and their parents. Parental permission must be obtained for research involving children “in accordance with and to the extent that consent is required by 45 CFR 46.116.”

The ages, maturity, and psychological states of the children involved in the research should be taken into account when determining whether children have the capacity to assent. This determination is made by the IRB. The IRB may require that investigators conduct an individual assessment of each child's ability to assent or may make a general determination for all children involved in the study.

The content and language of the assent process should be appropriate to the age and education/developmental stage of the children providing assent. It may be necessary to have multiple assent documents or assent processes if the children to be enrolled in the research are of different ages or at different stages of development. The UW-Madison IRBs have additional information regarding the assent/consent requirements for children participating in research, i.e., children over the age of 15 will have different requirements than those under the age of 6.

Refer to the HSIRB Website for more guidance on the assent and consent requirements for children: https://kb.wisc.edu/hsirbs/page.php?id=27037

Obtaining Informed Consent from Prisoners

Research involving prisoners requires approval by an IRB whose membership is specifically constituted to address the concerns of this vulnerable population per 45 CFR 46.304.

The DHHS regulations (45 CFR 46, Subpart C) require additional protections for prisoners who are involved as participants in research because they may "be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research."

The requirements specific to informed consent for prisoners are:

- "Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired"
- "Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole"

Therapeutic Misconception

Some research studies include examinations, diagnostic tests, and/or interactions with healthcare providers in addition to research or investigational interventions. While it is often appropriate to include treatment procedures in the conduct of research studies, there is a risk that research participants may misunderstand the benefits of research if they think that potential benefits of participation in research are certain. This is called the **therapeutic misconception**.

Investigators should discuss the potential risks and benefits of research as part of the informed consent process to minimize the possibility of therapeutic misconception.

Therapeutic misconception is defined as "when clinical research subjects fail to recognize the ways in which research participation may involve the sacrifice of some degree of personal care" [Appelbaum, Lidz, Grisso 2004]. Subjects may believe:

- That the physician would not suggest participation in the research study unless they feel that it is good for them.
- The risks must be low because their physician would not recruit them for the study otherwise.
- Frequent confusions subjects have about clinical research include:
    - Not understanding the difference between personalized clinical care and the impersonal, more global goals of clinical research.
    - Not understanding the concept of **clinical equipoise**, i.e., they think that the investigator already knows the treatment is better.
    - Not understanding the concept of randomization.
    - Overestimating the benefits of clinical research, and underestimating the risks.
    - Difficulty understanding percentages and probability statements.

Community Consultation

For studies targeting a specific subject population, it is often appropriate to consult with members of their community before conducting research. For example, members of a community may feel stigmatized if a members of that community are recruited as participants in research that may reveal unpopular or dangerous traits.

In addition, some cultures believe it is not appropriate to obtain informed consent **solely** from the individual participants, because the individual's interests may be considered to be intimately entwined with their community's interests. The appropriate way to attain community consent may vary widely, but is often achieved through meetings with large groups of community representatives or community leaders.

F. Other Informed Consent Considerations

Waiver of Informed Consent

The DHHS regulations (**45 CFR 46.116(d)**) allow IRBs to waive or alter **some or all of the required elements of informed consent** if all of the following conditions are met:

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

Decisions about waivers of informed consent often concern the issue of **practicability**. Although practicability is not defined in the DHHS regulations, it is not sufficient for an investigator to argue that seeking consent would be time-consuming or incur additional cost. This decision is not up to the PI, but rather the IRB.

In some situations, a waiver of informed consent may be appropriate for a medical record review or for using existing data or specimens that can be linked to identifiable individuals. Specific decisions regarding practicability are made by the IRB.

Refer to the UW-Madison IRB website (https://kb.wisc.edu/hsirbs/) for more information regarding waiver of informed consent.

Correlative or Sub-Studies

Some studies include additional procedures to supplement the data collected to address the main study objectives. This may include the collection of additional biological samples, additional questionnaires/surveys, or additional study procedures. These additional procedures could be optional or required. If the additional procedures are optional, remind participants they can still participate in the main study even if they choose not to consent to the correlative portion. On

some occasions, the subject can indicate his/her wishes to participate in the sub-study procedures in the body of the main consent form, or they could be described in a separate consent form. If this is the case, ensure that the subject and person obtaining consent sign and date those consent forms, as well as the primary consent form.

There are also correlative or sub-studies that include procedures that are not optional. In these studies, if subjects do not want to participate in the correlative/sub-study procedures, they cannot participate in the main study. It is important to make this completely clear to potential subject during the consent process.

G. Updates to the Consent Form/Re-Consenting

Federal regulations require disclosure of significant new findings that develop during the course of a research study that could impact the subject's willingness to continue participation in the research study [45 CFR 46.115(a)(7), 45 CFR 46.116(b)(5); 21 CFR 50.25(b)(5), 21 CFR 56.115(a)(7)]. Significant new findings often result in changes to the consent form or protocol after subjects have signed the original consent document.

What Constitutes Significant New Findings Requiring Report to Subjects?

According to the Health Sciences IRB Office, significant new findings generally include, but are not limited to:

- Changes in potential or actual risks or benefits to subjects including:
    - Changes in standard of care, such that participation in research could increase risk to subjects, i.e., subjects would be deprived of the standard of care by continuing to take part in the research study.
    - Identification of new risks to subjects currently receiving the study treatment.
    - Identification of potential late-term effects for subjects who have completed study treatment.
    - Discovery that a life threatening or severely debilitating side effect occurs more frequently than previously expected.
- Addition or deletion of study procedures or change in required number of visits including:
    - Addition of safety monitoring procedures.
    - Addition of study procedures or new instruments or questionnaires.
    - Collection of new or different information from subjects.

- Substantive alterations to the treatment subjects expect to or currently receive, including:
    - The frequency of dosing is increased or decreased.
    - The route of study drug administration is altered.
- Substantive changes in potential costs or payments to subjects, including:
    - A drug previously paid for by the study funds must now be covered by insurance or the subject's personal funds.
    - Payment for or costs of study participation is increased or decreased.

IRB Review of Significant New Findings or Changes

In general, the HS-IRBs must review the new information to be provided to subjects prior to its dissemination, unless the information must be provided to subjects to eliminate an apparent immediate hazard to subjects or others. In the case where the new findings must be reported to subject before IRB approval can be obtained because of a potential immediate hazard, the researcher must report the dissemination of this information to the applicable IRB within 14 business days.

Significant new findings that the researcher proposes to disseminate can be submitted for IRB review using a Change of Protocol form. In the case of oral dissemination of new findings, the IRB must be provided with a copy of the script that to be followed when contacting the subject or that describes the information that will be conveyed to subjects. If subjects will be provided with written materials, these documents should be submitted with the Change of Protocol.

Re-Consent

When re-consenting is required, it should be performed in the same thorough manner as the initial consenting. The study team should take as much time and care in explaining the change(s) during the re-consent process as when the subjects were initially consented. The goal is to make certain the subject understands and can make an informed decision as to whether or not to continue participation in the study.

Consenters should take extra time to outline specifically what has changed, why it has changed, and ensure the subject wants to remain in the study in light of the changes.

- The subject and person obtaining consent must sign and date the new consent form. A copy of the newly signed consent form must be provided to the subject.
- The subject could decline further participation based on the changes, in the same way they can decline further participation at any time after the original consent process.

- The re-consent process should be documented in the same way as the initial consent process.

The presentation of significant new findings to subjects can be accomplished through various means, including the following.

- A telephone call to subjects to report the significant new findings. The telephone call can be documented in the research record regarding when and who provided the new information to subjects. This method is especially encouraged when verification that subjects have received this information is needed, and subjects are no longer being seen in person or a significant gap in time exists between when the new findings are discovered and the next scheduled visit with the subject. At times, a telephone contact may be required prior to the subject's next visit, at which time they will re-consent.
- A letter to subjects can also be used to report significant new findings. This mode of communication may be suitable for information that needs to be communicated to subjects who are no longer seen by the researcher in person and when the changes are neither not life threatening nor time sensitive.
- Significant new findings or changes of protocol can be conveyed via a consent form addendum. The use of an addendum is particularly encouraged for subjects already enrolled in a research study and when the significant new findings are the only change that would be made to the consent document or only a few changes are proposed. If a revised consent form will be used instead of an addendum, the revisions should be highlighted to draw subjects' attention to the new information.

Refer to the HSIRB Guidance regarding Re-Consenting subjects for more information: https://kb.wisc.edu/hsirbs/page.php?id=18663.

When Re-Consenting Subjects Should Not be Pursued

The HS-IRBs are aware that study sponsors often request or require researchers to present revised consent documents to subjects to sign ("re-consent") when they have been revised, regardless of the significance of the new information or change. In many cases, asking subjects to sign a revised consent form is inappropriate and may result in needless burden on the subject, presentation of irrelevant information to the subjects and potential dilution of the impact of significant new findings. Consequently, the HS-IRBs generally disallow re-consenting subjects

when the revisions to consent documents would not or could not affect the subject's willingness to continue participation in the research study.

Examples of situations the HS-IRBs would generally not approve re-consenting subjects include:

- The version number or date on the consent form have been revised and no other changes have been made.
- The expiration date on a consent form has been updated and no other changes have been made.
- A minor increase in number of subjects to be enrolled in the study.
- New risk information about the study drug is discovered that is not related to late effects and all subjects have completed study treatment, i.e., are past the relevant time period for the new risks.
- Addition of new study procedures or additions of study visits that do not pertain to subjects already enrolled in the study, e.g., changes made to screening procedures that only affect new subjects.

H. Subject Retention Begins at the Initial Contact

Retention of enrolled participants is critical to the success of every clinical research study. Building a solid relationship between the research team and the research subject will help ensure good communication and follow through for the duration of the protocol.

Behaviors that can influence subject retention begin before the subject enrolls in the study and throughout their participation.

During the informed consent process research staff should establish trust. It is essential to remain unbiased, neutral, and non-coercive. Encourage subjects to always contact staff if they have any questions or concerns.

- Use open-ended questions when communicating with the subject(s). Open ended questions begin with words such as "what," "where," "how often," "when," and "please describe." A few potential questions include:
    - What more would you like to know? NOT Do you need any more information?
    - What are your concerns? NOT Do you have any concerns?
- The study team should not ask subjects questions in a demeaning or accusatory way:
    - Did you understand what I read to you?

Chapter 8: Determining Subject Eligibility

Participants in clinical research studies can play an active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. Some research participants may depend on the medications and medical care they receive by participating in a study. People participate in clinical research studies for many reasons, and it is the responsibility of the research team to make sure that only appropriate subjects are enrolled in the research study.

A. Eligibility Determination

All clinical research studies have requirements describing who may or may not participate. The factors that describe who can participate in a study are called **Eligibility Criteria**. **Eligibility Criteria**, often referred to in the protocol as the Inclusion and Exclusion Criteria, specify the conditions that must be present (**Inclusion Criteria**) and the conditions that must NOT be present (**Exclusion Criteria**) for the potential subject to be eligible to participate in the study.

Following the **Eligibility Criteria** is an important principle of clinical research that helps to produce reliable results. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before participating in a study, the research subject must qualify for the study. Some research studies seek participants with illnesses or conditions to be studied, while others require normal volunteers. It is important to note that inclusion and exclusion criteria are not used to reject people personally.. Rather, the **Eligibility Criteria** is created to define subjects to whom the study questions are applicable and can safely enroll. The criteria are designed so an individual who doesn't meet the criteria for safety reasons (i.e., study participation may cause unacceptable risk to the subject) is excluded.

The subject's eligibility is determined or confirmed after the subject has signed the consent form. Eligibility is determined by following the inclusion/exclusion criteria in the protocol. Subjects must meet <u>all</u> eligibility requirements stated in the protocol. Specific timelines for eligibility criteria must be reviewed. For example, a subject must have a normal ECG report within the last 3 months. To ensure consistency, researchers should use an **Eligibility Checklist**. An **Eligibility Checklist** is a systematic list of all eligibility criteria used to indicate the criteria that the subject

meets/doesn't meet. The PI must sign and date the eligibility checklist prior to the subject being registered to the study to ensure that the PI has confirmed the subject's eligibility.

B. Pre-Screening Subjects

Pre-screening subjects, prior to the informed consent process, is allowed to determine if the subject may be potentially eligible based on "gross" eligibility criteria, such as disease status, disease site, gender, age, etc. This is done primarily through a review of medical records when patients are scheduled for a clinic visit. This type of activity requires a waiver of consent approved by the IRB.

Potential subjects may be identified by clinical care providers or by the study staff using major eligibility criteria (i.e. the subject has a diagnosis of the disease/condition under investigation). The procedures to contact the potential subject or subjects identified must be described in the IRB application.

An investigator may discuss study availability and/or the possible entry into a study with a prospective subject without first obtaining consent; however, informed consent must be obtained prior to the initiation and conduct of any procedures performed solely for study purposes, including those to determine study eligibility. The study team may use results from tests and procedures that have been performed as part of the subject's clinical care if it is described as such in the protocol and the IRB application.

C. Subject Registration/Enrollment

After the subject has completed all required screening procedures and his/her eligibility has been confirmed by the PI, the subject is ready for the next step in study participation. The next step could be a wash-out or run-in period, or receiving study treatment. At this point, the subject is most often considered enrolled and/or registered.

- Refer to the protocol for instructions on how to register/enroll study subjects.
- Each subject is provided with a unique sequence # or subject ID.
- Make certain to keep copies of all registration documentation in the research chart.

Chapter 9: Subject Safety: Adverse Events, Serious Adverse Events, Unanticipated Problems and Other Reportable Events.

Ensuring subject safety is the responsibility of all members of the study team. The identification and effective management of all types of adverse events is integral to providing human subjects protection. Clinical research staff has an ethical obligation to account for, and treat adverse events associated with the subject's participation in a clinical research study. Oversight and documentation of AEs that occur during subject's participation in a study is one of the most important aspects of conducting clinical research.

A. Adverse Events

According to US Federal Regulations *[21 CFR 312.32(a)]*, an **Adverse Event (AE)** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. GCP *[ICH GCP E6 1.2]* further clarifies AEs as any untoward medical occurrence in a patient or clinical investigation subject who had been administered a product; a causal relationship with this treatment does not necessarily need to be shown.

Untoward is always used when describing AEs. In the context of AEs, untoward means unfavorable. While untoward can mean "unexpected" in other contexts, we consider all unfavorable events AEs, and assess expectedness separately.

An AE can therefore be any unfavorable sign, including an abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, ***regardless of whether or not it is considered related to the investigational product.***

Specifically, AEs include:

- Clinically significant abnormal laboratory results
- Development of condition during study participation, such as a side effect or symptom
- Worsening of conditions present at study enrollment
- Worsening of the primary condition or diagnosis of the subject population.

B. Serious Adverse Events

A Serious Adverse Event (SAE) is an AE that results in any of the following outcomes:

- Death.

- Life-threatening.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability or incapacity.
- A congenital abnormality or birth defects.
- A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

Individual protocols may include additional criteria apart from the examples described above that would make an AE serious, for example if the AE occurred during a specific time period.

C. Identifying Adverse Events

There are several methods that can be used by the study team to solicit AE reports from research subjects. Keep in mind that the protocol may describe some types of AEs that must be solicited, such as those that would require a change in the study intervention or additional medical intervention.

Open-ended questions:

Members of the study team should ask open ended questions to prompt the subject to think of any symptoms that may have occurred. Examples of open-ended questions include:

- "How have you been feeling since your last visit?"
- "Have there been any changes in medical conditions or medications?"
- "Have you seen a doctor or nurse, or gone to the emergency room since we last spoke?"

However, it can be difficult for all members of the study team to consistently ask the same question(s) and prompt the same responses. The use of checklists or standardized questionnaires can help address inconsistencies.

Checklist of symptoms:

A checklist can be given to subjects to easily document any symptoms or side effects that they may have experienced since their last study visit.

Checklists should be used cautiously so symptoms are not "suggested" to subjects. The study team may consider adding many symptoms, some of which may not be expected, so the AEs reported are not biased only to those that are expected.

Standardized questionnaire:

The use of a standardized questionnaire helps ensure that all members of the study team inquire about AEs in a consistent fashion. The questionnaire could include either open-ended questions or specific symptoms that are being solicited.

There are other study documents that could also be used to help identify adverse events, or prompt the study team to inquire further.

Documents completed by the subject:

- Subject diaries, questionnaires, and surveys should be reviewed as soon as the subject returns them to the study team to allow the research staff to inquire about any handwritten notes that may require additional discussion.

Other study documents:

- *Concomitant medication log* - if the subject indicates that he/she took an additional medication for a period of time, or increased/decreased the dose of concomitant medication, it may have been due to an AE and should prompt additional discussion.
- *Subject medical records* - inpatient and outpatient visit notes should be reviewed to determine if any new problems are reported, or if there were any inpatient hospitalizations that may be considered a SAE.

When does the study team start asking about, and documenting Adverse Events?

The first time subjects are asked about AEs, and when AEs are first documented, could vary from one study to the next.

Some studies begin to inquire about AEs *after informed consent is obtained*, prior to receiving any type of study intervention, to capture an adequate “baseline” for comparison at future visits. If these symptoms are not identified prior to the study intervention, they could be inaccurately attributed to the investigational product or intervention if they are reported after the subject receives study intervention.

Other studies do not being inquiring about or documenting AEs until *immediately prior* to the subject receiving the study intervention. This method can also serve as a “baseline” and allows documentation of symptoms or side effects that are also not attributed to the study intervention.

Regardless of when you start recording adverse events, documenting any symptoms the subject is experiencing prior to the intervention will prompt the research team to inquire about the symptom at a later date to determine if has improved, remained stable, or worsened, all of which should be documented.

D. Recording Adverse Events

Regardless of how the events are initially identified, all AEs must be documented in the subject chart in the most complete manner possible. An AE log maintained in the research chart is the most efficient and effective method to consistently document AEs as they are reported. Be sure to allow an area on each row for the PI signature/initials and date to indicate his/her review and the date that the PI became of aware of the event. .

Each AE record should include:

- **Date reported to the study team**

  Most protocols outline how quickly an AE or SAE must be reported to the sponsor upon the PI learning of the event. Additionally, if the AE or SAE meets criteria for reporting to the IRB, the timeframe for reporting is also determined by when the PI learned of the event.

- **Adverse Event Description**

  A description of the adverse event must be recorded. The event causing the symptoms should be captured whenever possible (e.g. tibia fracture as opposed to “leg pain”)

  If the event causing the symptoms cannot be determined, the description should include clinical symptoms, not a general assessment (e.g., “diarrhea” or “nausea” rather than “the flu-like symptoms”)

- **Start and Stop (or End) Dates** must also be documented

- **Outcome of the Adverse Event**

  The outcome of each adverse event must also be documented. There are several ways to categorize the outcomes. Usually the outcomes are variants of the options; Recovering or

Resolving, Recovered or Resolved with sequelae or without sequelae. The protocol should specify how the outcomes will be categorized. It's also important to know if the adverse events will need to be reported directly to a coordinating center, or the FDA, as there may be specific requirements.

- **Grade, severity, or intensity assessment**

As discussed in the previous chapters describing the Roles and Responsibilities of the Members of the Research team, **only the PI or Clinical Investigator can assess the adverse event to determine the grade or severity.**

The protocol may specify criteria for determining severity, or may direct Investigators to use a particular source, such as the Common Terminology Criteria for Adverse Events (CTCAE) maintained by the NCI (http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx) to determine the grade or severity of the AE. Though it was developed, and continues to be maintained by NCI, it is a helpful tool for all researchers, regardless of the disease/condition under investigation, to use when determining which grade, or severity may be most appropriate.

The CTCAE uses the terminology "Grade". Non-cancer research studies often refer to the Grade as the Severity of the Adverse Event. The Grades or Severities are categorized as:

  - ***Grade 1*** (Mild) describes mild symptoms that may be clinical or diagnostic observations only. Typically intervention is not indicated for Grade 1 adverse events.
  - ***Grade 2*** (Moderate) describes an adverse event in which local or noninvasive intervention is indicated. A grade 2 adverse event is one that results in a limitation of the subject's instrumental Activities of Daily Living. Instrumental Activities of Daily Living refer to activities such as preparing meals, shopping for groceries or clothes, using the telephone, and managing money.
  - ***Grade 3*** (Severe or medically significant, but not immediately life-threatening) AEs that fit into this category are considered medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization may be indicated. Grade 3 AEs are those that result in a limitation of the subject's Self-care Activities of Daily Living. Self-care Activities of Daily Living refer to activities such as bathing, dressing and undressing, feeding self, using the toilet, and taking

medications. Grade 3 AEs could be categorized as SAEs, depending on the outcome.

- ***Grade 4*** (Life-threatening consequences, urgent intervention indicated)
- ***Grade 5*** (Death related to AE)

It's important to point out that not all studies utilize all 5 grades in their Adverse Event records because Grades 4 and 5 are considered SAEs, this information is likely captured by a separate mechanism. Grade 3 could also be considered an SAE depending on the definitions described in your protocol.

- **Seriousness**

Documenting if an AE is Serious can be done by using an Adverse Event Log with a Serious Column allowing you to indicate Yes or No. This may seem somewhat redundant, but this field serves as a mechanism to double check that the appropriate documentation is completed as necessary, if the event is an SAE.

Severe vs. Serious

- Severity is the degree to which the AE is affecting the subject, while seriousness is determined by the AE meeting specified criteria. For example, a subject may have a "severe" headache that limits his or her ability to provide self-care, but unless the criteria for "serious" are met, such as being admitted to the hospital, the condition is not considered serious. Conversely, a subject may experience mild chest pain (not severe) that requires admission to a hospital for observation, in which case it is considered an SAE.

- **Attribution**

Attribution is the determination of whether or not an AE is related to the subject's participation in the research, including relatedness to an investigational product or intervention.

Deciding how to document the Attribution of the adverse event first requires that you separate intervention from non-intervention studies.

If your study is a non-intervention study, you should indicate whether or not participation in the study or study procedures could be responsible or related to occurrence of the adverse event (procedures performed, treatment or drugs provided). See: Guidance on Reviewing

and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, Section III.B: Assessing whether an adverse event is related or possibly related to participation in research.

If your study involves an intervention, you should refer to the FDA guidance, "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" (taken from Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf). Additional information can be found in 21 CFR 312.

As referenced in the chapter describing the Roles and Responsibilities of the Members of the Research team, only the PI or Clinical Investigator can make the determination of attribution or relatedness of the adverse event to the investigational product or intervention.

It is important that this categorization be taken seriously, as the reporting requirements differ based on the attribution or relatedness decision.

Common options to categorize the attribution or relatedness of the AE are Unrelated, Unlikely, Possible, Probable, or Definite. There are studies that do not use all of the categories, or perhaps the exact terminology. The protocol should specify how the attribution will be categorized.

If the study is evaluating an investigational product, the study participation and related procedures attribution should be assessed separately from the investigational product.

- **Unrelated:** An Unrelated AE is one that is clearly NOT related

  An AE may be considered Unrelated if the subject did not participate in any study procedures or receive the study intervention, or if there is another obvious cause of the AE (for example, a car accident or other disease/condition)

- **Unlikely:** An Unlikely AE is one that is doubtfully related

  The coincidence of the AE with the conduct of study procedures or exposure of the investigational product or intervention should be assessed. An AE that continued while the intervention was interrupted or stopped, or if the AE resolved while the intervention

continued, may be categorized as Unlikely. If there is another more likely cause of the AE, the PI may determine that the AE was unlikely related to the subject's participation in the study or the intervention.

- **Possible:** A Possible AE may be related

If the timing of the AE is reasonably consistent with the conduct of study procedures or exposure to the study intervention, and there is another cause of the AE that could be *equally likely*, the PI may categorize the AE as Possible.

- **Probable:** A Probable AE is likely related

If the timing of the AE is consistent with the conduct of study procedures or exposure to the study intervention, and it is *more likely* that the AE was caused by the study or the intervention than not, the PI may categorize the AE as Probable.

- **Definite:** An AE categorized as Definite is clearly related

If the timing of the AE is definitely consistent with the conduct of study procedures or exposure to the study intervention and it is *most likely* that the AE was caused by the study procedures or intervention such as because a likley occurrence of the AE was expected based on the study documents (protocol, consent, etc.). In this case, the PI may categorize the AE as definitely related.

- **AE Category, or Toxicity**
  The Common Terminology Criteria for Adverse Events (CTCAE) uses standard terminology to prevent comparing free text descriptions that may include typographical errors. The CTCAE also categorizes adverse events into appropriate body systems. For example, an adverse event of diarrhea would be categorized as a gastrointestinal disorder. This categorization allows the grouping and analysis of AEs by category. This categorization is also referred to as Toxicity. This categorization is required for studies under review of the UW Carbone Cancer Center, the ICTR Data Monitoring Committee (DMC) and Study Monitoring Service (SMS).
- **Expectedness**

  It is necessary to document if the adverse event was expected or unexpected.

  - **Expected**

An adverse event is considered expected if the event is included in the protocol, consent form, investigator brochure, investigational drug brochure or package insert as a known side effect or risk based on the subject population, the study procedures or study intervention. The event is considered expected if it is consistent with the frequency and severity of the risk as described in the documents referenced above.

- **Unexpected**

An adverse event is considered Unexpected if the event is NOT included in the documents referenced above, or if it occurring at a frequency or severity that is unexpected.

- **Treatment**

Adverse event records should include documentation of the treatment the subject received, such as medication or non-medication treatment. If there was no treatment administered, the option of None should be selected.

- **Action Taken**

Adverse event records should also include documentation related to the action taken with regards to the investigational product, such as a change in drug dosage, or if the subject was taken off the investigational product for a period of time (interruption). If there were no changes, the option of None should be selected.

An AE Tracking Log template can be found in the Case Report Form/Source Document Templates section of the Clinical Research Toolkit (https://ictr.wisc.edu/clinical-research-toolkit/)

E. Reporting Adverse Events

All AEs need to be reported to the PI or Clinical Investigator delegated the task of assessing AEs to determine the grade, severity and attribution; but deciding whether or not to report an AE beyond the study team can be difficult.

Refer to the protocol to determine when outside entities, such as the medical monitor, the DSMC, a coordinating center, or the sponsor or funding agency should be made aware of AE. If the study is funded by NIH, reporting requirements and timelines for reporting can vary by institute. It is important to note that the sponsor or protocol reporting requirements are DIFFERENT from IRB reporting requirements.

In addition to knowing to whom and when safety reports are made, study staff should be aware of when it is appropriate to include PHI and when it is not. For example, an IRB submission of a reportable event should **not** include PHI.

Requirements for reporting Adverse Events to the IRB

If the AE is considered an **Unanticipated Problem (UP)**, it must be reported to the IRB. An **Unanticipated Problem (UP)** is an event that meets the following criteria:

- The event is PROBABLY or DEFINITELY RELATED
- The event is UNEXPECTED. As a reminder, an event is considered unexpected if it was not described in the protocol, investigator's brochure, investigational drug brochure, package insert, IRB application, or informed consent document. It is also considered unexpected if the frequency or severity of the event is greater than expected.
- Another factor to consider is if the event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

However, there are exceptions to every rule and sometimes an AE will be EXPECTED, yet UNANTICIPATED for other reasons, such as the frequency or severity of the event in unexpected. The FDA provides an example list of these types of situations in this document: (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf)

Reporting requirements may vary, depending on the IRB of record. An event that is unexpected, probably or definitely related, and immediately life-threatening to study subjects, must be reported to the HS IRB within one business day of learning of the event. If it is not immediately life-threatening, but meets the other criteria, it must still be reported to the HS IRB, but the timeframe for reporting will be 10 or 14 days, depending on the type of event.

The HS IRB has developed a decision tool available on their website for study teams to use to help them determine if the event must be reported.
http://kb.wisc.edu/images/group78/18324/AEdecisionguidewithFDAVAupdate2.6.13.pdf

Safety Reporting to the FDA

It is important to know who is responsible for safety reporting to the FDA. Per 21 CFR 312.32(c)(1)(i), "The sponsor must report any *suspected adverse reaction* that is both *serious* and *unexpected* (to the FDA and all participating institutions)." For an investigator held IND, the investigator may be a sponsor-investigator assuming the additional responsibilities of the sponsor.

According to the FDA Guidance on Safety Reporting for INDs and BA/BE Studies (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm227351.pdf), deciding whether an AE meets the definition of a *suspected adverse reaction* is usually the most difficult determination, but this decision is critical to avoid the submission of uninformative IND safety reports. An AE is a *suspected adverse reaction* only if there is evidence to suggest a causal relationship between the drug and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure, e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome;
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug, e.g., tendon rupture; or
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events are occurring more frequently in the drug treatment group than in a concurrent or historical control group

Timelines for reporting to the FDA:

- The event must be reported no later than 15 days after learning of the event - If the event is **Serious**, **Suspected** and **Unexpected**
- The event must be reported no later than seven days (7) after learning of the event - If the event is **Life-threatening or Fatal**, **Suspected,** and **Unexpected**

There are several ways to report AEs to the FDA:

Annual Progress Reports: The IND or IDE holder is required to submit annual reports to the FDA (21 CFR 312.33) on the progress of the clinical investigations. The annual report should include a summary of all adverse events.

Safety Report: The IND or IDE holder must report all AE that are caused by or probably caused by the product under investigation. If the AE is alarming, the investigator shall report the AE immediately (within 24 hours of the investigator learning of the event).

Final Report: The IND or IDE holder must submit the final report shortly after completion of the investigation (21 CFR 312.64)

Safety Reporting in Studies with FDA Approved IND Exemption

For an investigational drug study that is not being conducted under an IND, i.e. the study meets the FDA IND Exemption criteria, the FDA guidance states that post marketing safety reporting requirements still apply (21 CFR 310.305, 314.80, and 600.80). In this case, the FDA should still be notified by the manufacturer, packer, and/or distributor of a marketed drug of serious, related, and unexpected adverse drug reaction.

Outside Safety Reports

An Outside Safety Report (OSR) is a report sent by a sponsor or IND holder that details an SAE occurring at another site involving the same study drug.

The OSRs may be routed differently depending on how each department or research program is set up to handle them.

- PIs are expected to review all OSRs and corresponding action letters that relate to their study.
- If the action letter states the AE changes the risk/benefit ratio of the study, it will need to be submitted to the IRB with consent form changes.

Reporting OSR to the IRB

- If significant safety issues are identified that alter the risk:benefit ratio, the IRB should be promptly notified via a New Information submission.
- If the event requires a revision to the informed consent form document in response to an OSR action letter, a change of protocol must be submitted to the IRB promptly, along with the OSR.

Even if the OSR does not meet the criteria above, if the information is relevant to the study it may need to be submitted to the IRB using the New Information report.

F. Reportable Events: Noncompliance

Noncompliance is defined as the failure to follow the federal regulations, state laws or institutional policies relevant to human subjects research, or the IRB-approved protocol.

The most common type of noncompliance occurs is a violation of the conduct of an IRB approved protocol. The research team should not conduct any procedures, visits, or interactions that are not specified in the IRB approved protocol. If changes in the research are necessary for the conduct of the study, a change of protocol must be submitted to and approved by the IRB prior to implementing the change. The one exception to this rule is when an immediate change is necessary to eliminate an apparent immediate hazard to the study subjects. If this occurs, it must be immediately reported to the IRB.

Failure to follow any of the following protocol activities as they are outlined in the approved protocol would result in noncompliance:

- Recruitment Plan
- Informed Consent Process
- Inclusion/Exclusion (Eligibility) Criteria
- Randomization or Un-Blinding Procedures
- Procedures & Study Interventions
- PI / Medical Oversight
- Data & Safety Monitoring Plan

For more detailed information on noncompliance and IRB reporting requirements, refer to the HS IRB website (https://kb.wisc.edu/hsirbs/) and click on the *Reportable Events* link on the left side menu bar.

G. Reportable Events: New Information

Researchers are expected to report new information to the IRB that affects the risks, benefits, or alternatives to study participation. New information is a “catch-all” category for identification of unanticipated risks or findings that may affect a subject’s willingness to take part in or continue participating in the study, and which may possibly lead to changes of protocol.

Some examples of new information that would require reporting to the IRB include:

- Changes in study status that are NOT specified in the protocol, e.g., early closure of a study, unexpected halt to enrollment due to safety concerns, etc.
- Revised package inserts.
- Recent publications related to the study, study intervention, or subject population that contains information that could have an impact on the subject's willingness to continue participating.

For more detailed information on new information and IRB reporting requirements, refer to the HS IRB website (https://kb.wisc.edu/hsirbs/) and click on the *Reportable Events* link on the left side menu bar.

Chapter 10: Subject Data Collection and Management

A. Data Collection and Data Management

While the extent of study data collection and management can vary study to study, study team members often feel that no matter how detailed they are, it is perceived as inadequate. That is a common frustration, and often times a misperception.

Study team members must focus on the collection of the critical data elements to avoid being overwhelmed collecting unnecessary data. If the critical data is not collected, or collected in an inconsistent, unstandardized manner, data integrity could be compromised and the study may never meet objectives.

The FDA and ICH GCP require accurate, complete, and up to date clinical research documentation and accurate records of all observations of each subject participating in the study. **Documentation** is the recording of all activities relating to the conduct of the research study and serves to substantiate the integrity of the data, confirm observations that are recorded, and verify the existence of subjects. Whether writing notes in a research chart, completing study worksheets and checklists, entering information in an electronic medical record, or collating communications (including email and telephone correspondence), documenting these activities is of the utmost importance.

Without documentation, there is no data. Study documentation serves as a way to verify all activities were completed as described in the protocol, ensure data integrity, and provide critical information to an auditor or monitor. Every step, from initial screening to last contact with a research subject must be verifiable.

The research staff should maintain the following records accurately and completely in real time:

- Records of receipt, use, or disposition of a device or drug.
- Records of each subject's case history (to be described in more detail later this chapter) and exposure to device or drugs.
- All relevant observations, including records concerning adverse drug or device effects.

If it is not documented, it did not happen.

Refer to the UW ICTR Clinical Research Toolkit for a Subject Chart Table of Contents template (PDF): ictr.wisc.edu/CRToolkit

B. Privacy and Confidentiality

There are privacy and confidentiality expectations when managing subject data and study records in a healthcare setting.

Subject data collected and managed for research can vary depending on the nature of the study. Some researchers need to work with identifiable information, while others can work with subject data that has been de-identified. Knowing the correct terminology for the identifiability of subject records is important:

- **De-identified data:** Data that have been stripped of all subject identifiers, including all HIPAA identifiers. If the data includes an indirect link to subject identifiers, e.g., via coded ID numbers, then the data is considered by the IRB to be coded, not de-identified. Please note that data can be considered de-identified under the Common Rule, while NOT de-identified under the HIPAA Privacy Rule.
- **Directly Identifiable Data:** Information identifying subjects is stored directly on data records.
- **Indirectly Identifiable Data:** Information identifying subjects is linked to data record, but stored separately.
- **Coded data:** Coded data is stripped of all direct subject identifiers, but each record has its own study ID or code, which is linked to identifiable information such as name or medical record number. The linking file must be separate from the coded data set. The code itself should not contain identifiers such as subject initials or medical record number.
- **Anonymous Data:** Anonymous data contains no direct or indirect links in the data record.

The need to maintain confidentiality of private information, and of information that can be used to identify a particular individual, exists in virtually all studies in which data are collected from or about living individuals. In most research, maintaining confidentiality is a matter of following some established practices, for example:

- **Limiting access to records and documents that contain identified data -** It is important to know the measures that will be implemented by your research team to prevent access to the identifiable subject information by unauthorized individuals, including paper and electronic forms of information.
- **Storing research records in locked cabinets and/or secured databases -** Consideration must be given to how data will be stored, transported, used, or displayed on laptops or portable devices, on computers, or on servers managed by someone other than the research institution. Additional safeguards that may need to be in place (e.g., link for coded data stored separately, de-identified data) to protect data from risk of breach of confidentiality, such as theft of a laptop, or loss of portable device. Staff should consult with their IT department about the necessary data security measures to be taken.
- **Taking measures to prevent accidental or premature destruction of these documents -** When considering record storage needs, take measures to prevent loss of data, or accidental or premature destruction.

C. Source Documents

The source data is the foundation of all clinical research studies. Not only do the source documents confirm complete and accurate data collection, but they also give tangible evidence that the study was conducted in an ethical manner according to the protocol.

Definition: A source document is the first place an observation or data point is recorded. Per ICH GCP E6 1.52, source documents are defined as “Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)”.

Examples of source documents include:

- Medical records, including inpatient and outpatient clinic visit notes
- Subject visit notes, flowsheets, physical exam notes, checklists, and AE lists
- Vital sign measurement recordings

- Clinical dictations, or notes taken during interactions with the subject
- Signed consent form(s)
- Investigational product dispensing and administration records
- CT scans, X-rays, and MRI films and reports
- Laboratory, pathology, and surgery reports
- Subject-completed diaries, questionnaires, and surveys
- Inclusion/exclusion (eligibility) checklist
- Study-specific worksheets or checklists

Electronic Source (eSource) Documentation

"With the use of computerized systems for capturing clinical investigation data, it is common to find at least some source data recorded electronically. Common examples include, but are not limited to clinical data initially recorded in electronic health records maintained by healthcare providers and institutions, electronic laboratory reports, digital medical images from devices, and electronic diaries completed by study subjects."

According to the September 2013 FDA guidance titled "Electronic Source Data in Clinical Investigations", (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf]) "When original observations are entered directly into a computerized system, the electronic record is the source document".

In some cases, the electronic record may need to be printed, for instance to allow a clinical investigator to document the clinical significance of abnormal laboratory findings. It is important to remember that even if the data from the electronic record is not printed, the investigator is responsible for providing auditors with access to the records that serve as the electronic source data. This statement is true for internal and external auditors and inspectors, i.e., FDA.

D. Case Report Forms

Definition: A Case Report Form (CRF) is a standard form used to capture protocol-required data in a consistent manner (paper or electronic, referred to as an eCRF).

CRFs are the key document management tools used in clinical research studies to collect the protocol-required data in a standardized, consistent format. The data obtained must be usable

and it is the responsibility of the study team to ensure all CRFs are legible, accurate, and complete.

They also provide increased efficiency in processing and analyzing data. When studies are conducted at more than one site, CRFs allow the merging of data between sites.

If the CRF is the first place a data element is recorded, it is also serving as the source document. This is common for documents that are completed by the subject, such as questionnaires, surveys, or diaries. It is also permissible in some circumstances for study staff to enter data directly into a CRF or eCRF without first recording the data elsewhere, e.g., vital signs. This determination needs to be made prior to IRB submission and described in the protocol.

Some research studies will outline how to correct errors made in the CRF. It is standard, best practice to correct an error in the CRF by lining through the incorrect data with a single line and write the correct information above. Include your initials, date, and the reason for the change.

Correcting data that is managed in electronic format can vary depending on the software and the monitoring processes in place for the study.

Electronic Case Report Forms (eCRFs)

The FDA defined eCRFs as instruments that serves as “an auditable electronic record of information that generally is reported to the sponsor on each subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analyzed, and reported.”

According to the September 2013 FDA guidance titled “Electronic Source Data in Clinical Investigations” (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf), “Many data elements, e.g., blood pressure, weight, temperature, pill count, resolution of a symptom or sign …, (are) obtained at a study visit and can be entered directly into the eCRF by an authorized data originator if the study meets the 21 CFR 11 requirements. This direct entry of data can eliminate errors by not using a paper transcription step before entry into the eCRF. For these data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for FDA inspection” and other auditors as applicable.

There are additional steps that must be taken to meet 21 CFR 11 requirements. There are secure, auditable electronic data capture systems that meet these requirements. Standard spreadsheets such as Microsoft Excel do not meet these requirements, and cannot be the first or only place research data is collected and managed.

E. Case/Medical Histories

The FDA refers to subject records and documentation as "Case/Medical History." Regardless of the format, paper or electronic, *"An investigator is required to prepare and maintain adequate and accurate case histories that record **all observations and other data pertinent to the investigation on each subject**" (CFR 312.62).*

- Case history is a broad term used by the FDA to describe the CRFs and supporting source documents, including signed and dated consent forms and medical records, i.e., progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.
- Case histories could be the only source of this information.

Required documentation in clinical research includes records of:

- Informed Consent Process
    - The case history for each individual should document that informed consent was obtained prior to participation in the study. This process could be captured on a separate source document or be part of the initial visit progress note.
- Medical history, often used as documentation to confirm the subject met the study eligibility criteria.
- Physical examination
- Investigational product accountability records
    - Investigational product dispensation, administration, and accountability records must be maintained.
- Adverse event records (with grade/severity and attribution)
    - Records related to adverse events should be included in the subject's research chart. This is most often done using an AE log identifying the grade or severity and attribution, but it could be handwritten observation notes or medical records if the subject was seen at another location.
- Subject correspondence
    - Correspondence with the subject should be documented in the subject's research chart. The study records should also include correspondence with other entities

about the subject, for example communication with the coordinating center, CRO, or sponsor.

- Documentation of noncompliance
    - Any deviation from the protocol should be documented. This could be done by using a standard deviation form, or this could be documented in handwritten notes.

F. Note to File

A Note to File (NTF) is a document that can be used to describe minor discrepancies or deficiencies that document the research staff's acknowledgement and potential explanation of the error or deficiency.

Adding an NTF *does not correct the error or ensure compliance*, it simply allows additional information to be provided that would help someone else looking at the records to interpret the discrepancy or deficiency. An NTF could be used to document the reason for missed procedures, documents, or data, or to explain why there were protocol deviations.

NTFs should be kept to a minimum. A significant number could be a red flag for an individual not involved in the conduct of the study, giving the impression that the study was not conducted with the attention it needed.

What a Note to File is:

Documentation of missing or incomplete data. An NTF does not justify the missing data, but rather allows independent individuals to accurately reproduce the trail of the study data.

Documentation of an error in record keeping. An NTF could be documentation of an error in record keeping, or missing records. For example, if the subject didn't return their diary because they lost it.

Explanation of how information was obtained or made available. An NTF could be an explanation of how information was obtained or made available.

Clarify discrepancies. An NTF could clarify discrepancies. For example, if the subject forgot to bring unused study medication to their visit and mailed it instead, the NTF could explain why the date of drug return was a date other than the study visit.

Reference to other documentation. An NTF could explain that the subject's visit occurred outside the study visit window because the subject was on an extended vacation. The NTF could also refer to the email sent by the subject in the correspondence section of the research chart.

Explanation that the apparent missing records are stored in a different location. If the clinical investigator identified a problem during the conduct of the physical exam, a NTF could be added to the AE section of the chart to reference the physical exam note.

What a Note to File is not:

The source document. An NTF cannot be used in place of the source document. It can be used to explain why the source document is missing, or filed in a separate location, but cannot replace the source.

Only record of a deviation or noncompliance event. An NTF does not replace the standard documentation of a deviation or noncompliant event, but rather, could be used to clarify or explain the deviation in more detail.

A Note to File should:

- **Be generated on a case-by-case basis.** Templates should not be created.
- **Include the date the NTF was written, subject ID, and the study title, with IRB number and PI name.**
- **Be legible if handwritten.** The document should be legible if handwritten.
- **Clearly explain the reason for the error, omission, or discrepancy and the process it aims to address.**
- **Be signed and dated by the individual who is writing it and the PI (if applicable).**
- **Include any corrective and preventive action or follow-up, when applicable.**
- **Be filed with the subject document it refers to.**

An NTF can help someone, such as an auditor, looking at the records to interpret the discrepancy or deficiency and to trace the trail of events to recreate the data. An NTF could also be detrimental if not accurate and complete. For example, an NTF that only includes a statement that the subject did not receive the study drug could raise more concerns and questions, rather than explain a deficiency or deviation.

G. Electronic Data Management

When storing study data electronically, there is additional guidance that should be considered.

ICH GCP 5.5 (Trial Management, Data Handling and Record Keeping)

When using electronic trial data handling and/or remote electronic trial data systems, additional system requirements should be met:

- Ensure and document that the electronic data management system requirements have been thoroughly tested for completeness, accuracy, reliability, and consistent intended performance, referred to as validation.
- Maintain SOPs for using these systems.
- Ensure that the system has an audit trail. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data. This means that an edit record or audit trail must be maintained to demonstrate when the data was entered and verified, and all changes along the way.
- Ensure that the system prevents unauthorized access to the data.
- Maintain a list of the roles or individuals who are authorized to make data changes. Maintain adequate backup of the data.

Best practices:

- Electronic data management options should be explored for the reasons mentioned above. Researchers are discouraged from using a spreadsheet program to enter and maintain study data. A secure system designed for managing study data, such as a clinical trial management system (OnCore) or an electronic data capture system (REDCap) is more appropriate.
- If the only option is a spreadsheet, do not include identifiers, such as subject names and medical record numbers.

H. Study Drug Dispensation, Administration and Accountability

The “investigator is responsible for … the control of drugs under investigation” (21 CFR 312.60). This means the investigator must maintain records of the product's delivery to the site, the inventory at the site, the use by each subject, and the final disposition of the study drug, i.e., return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates if applicable, and the unique code numbers assigned to the investigational product(s) and study subjects. Investigators should

maintain records that adequately document that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor (ICH GCP 4.6.1, 4.6.3).

“Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution’s duties for investigational product(s) accountability at the study site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution” (ICH GCP 4.6.2). Per UWHC Administrative Policy 4.11 “Investigational and Study Drug Control”, all UWHC clinical research studies involving a drug must be coordinated through the Pharmaceutical Research Center (PRC). (*Refer to Chapter 12: Clinical Research Resources for more information on the PRC)*

Investigators conducting clinical drug studies must contact the PRC in advance for each clinical drug research project to obtain an institutional feasibility assessment, Pharmacy/PRC budget estimate, and to determine drug handling requirements. Study drugs will be handled (defined as receipt, storage, preparation, dispensing, and destruction) by the pharmacy/PRC or PRC-approved delegate. At its discretion, PRC may delegate study drug handling activities to the investigator if both the study and investigator meet specific PRC delegation criteria and sponsor approval. Such delegation will be confirmed in writing and stipulate the conditions under which the delegation is being awarded. Delegated studies require PRC involvement prior to subject enrollment and may be audited for compliance with study drug distribution procedures and institutional policy throughout the study.

Within this chapter, the terms dispensation, administration and distribution are defined as follows:

- **DISPENSATION:** the pouring or placing of drugs from stock supplies into bottles or containers; the labeling of such items with the patient's name, medication, dosage and directions; and the giving of such bottles or containers to personnel for administering to patients.
  Dispensing medication requires a licensed pharmacist who is responsible for preparation and labeling of the medication. After preparation and labeling, the pharmacist's role in the research setting most commonly includes providing the medication to either the distributor or licensed personnel who will administer the medication.

- **ADMINISTRATION:** Administration of medication refers to executing the instructions, i.e., physician orders, for medication delivery. It is the act of providing medication to the participant and either observing the intake or active delivery of the medication via injection or another specified route. If the medication requires delivery through an IV, it requires licensed personnel specifically trained in medication administration.

  The five rights of medication administration are applicable to all clinical research studies that involve a drug.
  - Right drug
  - Right client (research participant)
  - Right dose
  - Right route
  - Right time

  Most often, a non-licensed CRC does not **dispense** or **administer** the investigational product, but rather, **distributes** the study drug to subjects based on the instructions in the protocol, i.e., following blinding and randomization rules as applicable.

- **DISTRIBUTION:**
  - Distribution of medication is the act of providing (packaged) medication to the research participant. For packaged medication, the subject is most often instructed to self-administer the medication at future date(s).
  - When distributing medications to research subjects, it is the responsibility of the individual distributing the study drug to ensure the correct medication is given to the correct research subject. The five rights of medication administration (described above) can also be applied during the process of medication distribution and will provide the systematic approach needed to ensure safety to the participant and adherence to the research protocol. Using a systematic approach each time and strict adherence to each step cannot be over emphasized. Omission of one step may cause an error to occur.

- **LABELING:**
  - Labeling of medication will vary depending on the research protocol's specific instructions, but there are some requirements that apply to all investigational

drugs. According to 21 CFR 312.6(a), “the immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." In addition, “the label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated” (21 CFR 312.6(b)).

- During study initiation, it is important to meet with representatives from PRC to discuss the information that will appear on the medication label. This will help to determine how best to verify the right medication was distributed to the right subject.

Tips for Distributing Medication to Research Subjects:

The study staff distributing medications should:

- Verify the medication and participant's information with another staff member prior to dispensing the medication to the participant. This requires that both staff members check the participant's name and/or identification number, medication name, dose, and route of administration.
- Verify patient information on the label.
    - When medication is distributed to the participant, the participant should state two unique identifiers aloud, while study staff read and re-verify information on the medication label.
    - Have the participant spell their name, state their subject number, or date of birth. It is important that the subject gives the information aloud instead of verifying a statement by staff. It is not enough to ask the person "is your name _____." If the participant has an arm band, check it against the medication, also.
- Verify drug information on label including drug name, strength, formulation, and quantity.
- Verify protocol number.
- Verify any drug-specific ID# number (kit# or bottle number), if applicable
- The point of transfer to patient is the last in the line of checks to ensure correct distribution of medication. If there are any doubts about the correctness of the medication, the process should be stopped immediately and rechecked.

- Provide written instructions to the participant regarding dosing time, number of pills or capsules, and route of administration. It is good practice to have the participant read through the instructions and repeat the information back. “The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly” (ICH GCP 4.6.6). Appropriate actions should be taken to ensure study drug compliance.

Errors

“The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol” (ICH GCP 4.6.5). Medication distribution errors are serious. Such an error may cause an AE in a study subject, cause the subject to be disqualified, or the subject's data to be eliminated from the analysis. In some instances, it may result in the study being suspended.

When distributing medications to participants, it is important to ensure the correct medication is given to the correct research participant. It is impossible to be too careful when distributing medications to study participants. When an error occurs, it is the responsibility of the study team to report the occurrence to the PI immediately. He/she is responsible for determining follow-up activities. It may be necessary to report the information to the IRB and the DSM group working with the study. In addition, SOP or guidelines for distributing medications specific to individual programs or departments may need to be addressed, as well.

I. Data Integrity: Ongoing Compliance Monitoring

Data collection is the process of accumulating and documenting all required study information and observations occurring during the defined study period. The importance of accurate data collection and documentation cannot be overemphasized. Members of the research team work hands-on gathering data for clinical trials, including recording information, reviewing medical records, obtaining, processing and storing samples, and much more. Research data and documentation must be accurate.

Every study should include a series of checks and balances prior to, during and after the conduct of a study.

Data Integrity: refers to maintaining and ensuring data is high quality (valid, accurate, and consistent). FDA guidance documents refer to the acronym **ALCOA** when determining data integrity:

Attributable: It should be clear who has documented the data.

Legible: It should be readable with identifiable signatures.

Contemporaneous: The information should be documented in the correct time frame along with the flow of events.

Original: The investigator should have the original source document.

Accurate: Accurate, consistent and real representation of facts.

Compliance: *[ICH GCP E6 1.15]* Adherence to all study-related requirements, GCP requirements, and applicable regulatory requirements.

There are several factors, such as excessive workload, that can help create situations where protocol deviations are more likely. Research personnel should balance their workload, ask for help when needed and delegate responsibilities when possible.

Mistakes and the unexpected will happen. Research staff must be resilient enough to overcome the obstacles that come their way, and not resort to falsifying or fabricating data…the over-all success of the study depends on it.

Establishing a process for ongoing self-assessments can help a study be “audit-ready” as well as ensuring that it meets the standards for conduct set by the institution, sponsor, and federal regulations. ICTR has developed a Self- Audit Tool available on the Clinical Research Toolkit webpage (https://ictr.wisc.edu/clinical-research-toolkit/).The tool can help assess study conduct in multiple areas including inclusion/exclusion, consenting documentation and process, and protocol adherence. This tool is for guidance only, and some of the items included on the worksheet may not be applicable to all studies.

Tips to verify consistency of CRFs with source documentation and other CRFs:

- If a subject is taking a medication for a specific indication, the indication should be included on the medical history form.
- If the subject takes a medication to treat an AE symptom, the medication should be included on the concomitant medication log with consistent start and stop dates.
- If symptoms are recorded at one visit they should be followed for the course of the study.

- If a subject completes a any kind of diary, the study team should query any handwritten notes to determine if AEs occurred.

The Self-Audit tool, available on the UW ICTR Clinical Research Toolkit webpage (https://ictr.wisc.edu/clinical-research-toolkit/) can prepare members of the study team for an audit by helping them look at study documents in the way an auditor would.

What do auditors inspect?

- All IRB correspondence (submissions, email correspondence, etc.).
- Dated, IRB-approved consent forms.
- Adherence to inclusion and exclusion criteria via individual subjects eligibility in source documents.
- AE, including those reported to IRB as necessary.
- Whether the study staff is following protocol.
- Whether the team is reporting any procedural changes.

Data Discrepancy is a difference between the source and the CRF (electronic and/or paper format), within a single document, or across documents (different source documents or CRFs).

When the study team finds discrepancies, there are procedures to follow to resolve the discrepancy in paper format:

- Draw one horizontal line through the error.
- Add/Insert the correct data.
- Initial and date the change.
- DO NOT ERASE, scribble out, or use correction fluid or any other means that could obscure the original entry.

Resolving discrepancies in an electronic format can vary depending on the software and the monitoring processes in place for the study.

Ongoing Compliance Assessments Available Through UW ICTR

The US ICTR Study Monitoring Service (SMS) program focuses on serving the needs of UW research professionals by identifying areas of improvement and providing assistance to address them.

The goals of the UW ICTR SMS efforts are to:

- Implement capacity-building strategies to realign compliance and research integrity.
- Ensure the rights and well-being of research subjects; ensure compliance with federal, state, local and institutional regulations and guidelines.
- Facilitate effective working relationships with and between investigators, his/her staff, and applicable university oversight.
- Promote collaboration of compliance initiatives within and across the clinical research infrastructure at UW-Madison.

The objectives of the SMS Program are to:

- Develop and maintain mechanism(s) to receive and review requests for compliance reviews.
- Conduct reviews to ensure compliance with GCP guidelines, in conjunction with the provisions of IRB-approved protocols, and federal, state, local and institutional regulations.
- Work closely with investigators and research support teams to address areas of improvement that have been identified.
- Develop and distribute clinical research compliance materials to serve as guidance for institutional, investigator, and research support staff.

UW ICTR Study Monitoring Services available to assist with ongoing compliance monitoring:

Study Monitor of Record

Upon request by the PI or PI Designee, the Study Monitor of Record (SMoR) service can be contracted to satisfy independent study monitoring requirements in accordance with FDA and ICH GCP standards. Acting as a SMoR includes ongoing monitoring of study data, study documentation and subject safety throughout the life cycle of the study.

Routine Review (RR)

A routine review is a one-time QA review. Protocols will be randomly for routine review and prioritized based on risk assessment score. Protocols may be scheduled for repeated audits based on compliance results.

Directed Review (DR)

A directed review is a one-time review conducted on a For Cause basis, at the request of an administrative official, entity, or agency.

Ongoing Compliance Assessments within the UW Carbone Cancer Center

The UWCCC Clinical Research Compliance Office (CRCO) provides compliance, oversight and monitoring for clinical research infrastructure of the UWCCC.

CRCO staff manage several programs and ongoing initiatives:

- Protocol Review and Monitoring Committee
- Data and Safety Monitoring Committee
- Training for new staff and Continuing Education for current staff
- Protocol registration compliance (CT.gov and Clinical Trials Reporting Program)
- Affiliate and Outreach services, including multisite coordination and oversight of the Wisconsin Oncology Network

In addition, the CRCO staff conducts various types of compliance reviews: Quality Assurance Reviews (QARs), Internal Audits (IAs) and Response Reviews (RRs).

UWCCC Quality Assurance Reviews

Quality Assurance Reviews (QARs) are performed on all investigator-initiated trials (IITs) and cooperative group protocols after the first two subjects have been accrued to the study or within 6 months after first patient is accrued. QARs are performed by the QA coordinator and consist of regulatory, case review, and database checks. They are designed to identify, early on in the study, any potential problems.

UWCCC Internal Audits

Internal audits (IAs) are conducted once per year on all IITs conducted at the UWCCC and its affiliates. During an IA, the compliance team will review:

- A select number of subject cases for protocol compliance and documentation.
- Regulatory documents for adherence to regulatory guidelines, reporting of SAEs, approval of protocol amendments, etc.
- Drug accountability records.

An internal audit report is generated and sent to the PI. If follow-up is required, a Corrective and Preventive Action plan is put together by the PI to address any deficiencies that were cited in the audit. The Corrective and Preventive Action plan is sent to the CRCO and the DSMC reviews it at their next meeting and determines if it is acceptable.

UWCCC Response Reviews

The standard UWCCC Data and Safety Monitoring Plan (DSMP) provides an independent response confirmation as part of its ongoing QA program. A Response Review (RR) is performed on any confirmed radiological partial response or complete response, as defined in the protocol, on any therapeutic trial that does not have an external review bod such as an IIT.

- When the investigator believes the best response has been achieved, an independent RR is completed by an impartial UWCCC investigator. A system is in place to mitigate if the review does not concur with the reported response.

Consequences of Improperly Collected or Documented Data

- Inability to answer research questions accurately.
- Inability to repeat and validate the study.
- Distorted findings resulting in wasted resources.
- Dissemination of misinformation nay lead other researchers to pursue fruitless avenues of investigation.
- Compromised public policy decisions.
- Potential for harm to human participants and animal subjects.
- Investigators participating in academic misconduct or fraud may lead to loss of job, reputation, or legal prosecution.

Don’t hesitate to ask. For clinical research compliance-related questions, contact the ICTR SMS team by emailing compliance@lists.wisc.edu or completing a consult request form through the UWICTR webpage (https://ictr.wisc.edu/ > select Free Consult Request from the top menu bar)

J. Research Sample and Specimen Collection, Handling, Processing and Management

Research samples and specimens should be collected as outlined in the protocol or the laboratory manual of procedures (MOP). If there are questions about specimen collection, they should be resolved prior to initiating the protocol.

Coded Private Information

Research with coded private information or specimens involves human subjects if:

- The private information or specimens were collected specifically for the currently proposed research project through an interaction or intervention with living individuals; or
- The investigator(s) can readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain.

Research with coded private information or specimens does not involve human subjects if:

- The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain.

Sample Quality

The quality of any laboratory test result is dependent on many variables, the first of which begins with the technician. The technician's care, skill, and knowledge when preparing the patient and specimen are essential to the provision of the highest quality standards for testing and services. The subject must first be properly prepared so that the best possible specimen can be collected. Next, the actual collection of the specimen must be completed. Then, the specimen should be properly processed, packaged and transported to the laboratory in a timely manner and under environmental conditions that will not compromise the integrity of the specimen. Preparing samples for testing is one of the most routine, yet most critical, processes to ensure accurate results in the clinical laboratory. Improperly handled samples can give misleading results and compromise the function of diagnostic instruments.

Health and Safety Precautions

Use universal precautions when handling specimens containing blood or other potentially infectious material. This includes proper personal protective equipment. This refers to protective clothing, nitrile or latex gloves, goggles, or other garments or equipment designed to protect the wearer's body from injury or exposure. Work areas contaminated with biological specimens must be disinfected immediately with 10% bleach (hypochlorite at 0.5% final concentration) or other approved disinfectant. In the event of an exposure, administer first aid immediately, notify a manager or supervisor, and seek prompt medical attention.

Specimens must be handled in a safe manner and according to applicable legal requirements or guidance. Information on safe specimen handling may be obtained from the U.S. Occupational Safety and Health Administration and the Centers for Disease Control and Prevention. In handling human specimens, the goal is to protect healthcare workers and ancillary staff, as well as the general public, from exposures to blood and to other potentially infectious body fluids. This includes all individuals involved in the transportation of specimens.

- All samples must be considered to be infectious.
- Use of “universal precautions” handling.
- Never assume any sample is “safe.”

Specimen Labels

All specimens should be labeled at the time of collection with a patient identifiers (usually a subject ID number), however additional information on the label may be site, department, or study specific. Be sure to check MOP directions for proper specimen labeling.

- A subject ID (or other unique code) is always required.
- Date of collection
- The second patient identifier may be one of the following:
    - Date of birth (month/date/year)
    - Other unique patient identifier also on the test requisition, e.g., hospital, office ID code, or file number
    - Requisition number or specimen barcode label
    - Other barcode labels can be used if barcode matches the unique identifiers on the printed requisition. The barcode does not need to be human readable.

NOTE: Location-based identifiers are generally not acceptable, e.g., hospital room number or street address.

If the label is hand-written, use an alcohol resistant pen. If glass slides are submitted, use a pencil for labeling the frosted end. When transferring a specimen to a container other than the tube used to draw the sample, e.g., transfer vials, also indicate specimen type on the label, e.g., serum, plasma, urine.

Packaging and Shipping

The federal government requires training and certification prior to shipping or transporting hazardous materials. The university requires this training of each person who will be shipping materials before shipping.

By law, anyone who packs, ships, transports, or receives dangerous goods must be trained to properly. The training is made available through the UW-Madison Environment, Health and Safety department (http://www.ehs.wisc.edu/hazmatshipping.htm) and includes how to:

- Identify and classify dangerous goods
- Package dangerous goods
- Label and mark packages
- Document shipments

The shipper bears ultimate legal responsibility and liability for properly performing these tasks. The following are the minimum specimen packaging guidelines that should be followed when submitting specimens.

- The hazardous material to be shipped must be placed in a securely closed, watertight, leak-proof, primary container with labeled contents. All specimen container caps and lids should be properly tightened to prevent leakage.
- Sufficient absorbent material should be included within the secondary container to completely absorb the contents in case of a spill. Several primary containers can be placed in a durable, watertight container that acts as a secondary container.
- Properly complete the requisition or required form, if necessary. An itemized list of contents should be placed between the secondary container and the outer package.
- Collect the specimen(s) and transfer to a proper transport container, if needed. Double check the specimen container to ensure it is not beyond its stated expiration date.

- If the specimen has been classified as an “infectious substance,” transport in a box designed to withstand 95kPa of pressure to meet national and federal shipping requirements, i.e., IATA, DOT. These boxes are available from local laboratory supply companies.

Frozen Specimens

Frozen specimens must be transported in insulated containers surrounded by an amount of dry ice sufficient to keep the specimen frozen until it reaches the laboratory. Thawed specimens are almost always unsuitable for analysis.

Dry ice is considered hazardous during transport for three reasons:

- Explosion hazard: Dry ice releases a large volume of carbon dioxide gas as it sublimates. If packaged in a container that does not allow for release of the gas, the package may explode, causing personal injury or property damage.
- Suffocation hazard: A large volume of carbon dioxide gas emitted in a confined or poorly ventilated space may create an oxygen deficient atmosphere.
- Contact hazard: Dry ice is a cryogenic material that causes severe frostbite upon contact.

Packages containing dry ice must allow for:

- Gas venting: Packages must allow for release of carbon dioxide gas. Dry ice must never be sealed in a container with an airtight seal.
- Package integrity: A package containing dry ice must be of adequate strength to withstand the loading and unloading normally encountered in transport. The package must also prevent any loss of contents that might be caused by vibration or by changes in temperature, humidity, or altitude.
- Package materials: Do not use plastics that can be rendered brittle or permeable by the temperature of dry ice. This problem can be avoided by using commercially available packages intended to contain dry ice.

Specimen documentation should include:

- While the samples are stored in a freezer, a temperature log should be maintained.
- Personnel should maintain records of shipping training that must be renewed every 24 months.
- Filling in and signing a shipment’s airway bill provides documentation of the shipment.
- Records of shipments should be maintained for two years following the shipment

Chapter 11: Clinical Research Resources

A. Ancillary Services

There are various entities within the UW-Madison clinical research environment that offer ancillary services. Many of the ancillary services groups primarily conduct services related to clinical care, but can also offer the procedures for clinical research, such as the UWHC Clinical Laboratory. In addition, there are groups that only offer services for the purposes of research, such as the ICTR Clinical Research Unit (CRU) and the PRC.

The specific ancillary services that must be consulted vary on a protocol-by-protocol basis, for example, a protocol that includes the use of an investigational will utilize the services offered by the PRC as an Ancillary Service provider. There are many ancillary service providers described below. The contact information for each of the Ancillary Services described below can be found at: https://kb.wisc.edu/ictr/page.php?id=24463.

Research Billing Compliance Program

UW Health is a world class academic medical center, and our family of caregivers works at the leading edge of clinical research. Every day, UW Health clinicians and patients are involved in hundreds of research studies.

Clinical research studies add a layer of complexity to clinical billing practices. The UW Health Research Billing Compliance Program works with researchers and other staff to ensure that we bill appropriately and follow the law.

The UW Health Research Billing Compliance Program strives to:

- Standardize the billing procedures used in clinical research.
- Centralize the review of research study budgets and protocols for compliance with the Centers for Medicare/Medicaid clinical trial billing rules.
- Streamline research billing processes with the UWHC and UWMF patient account offices.

Under Medicare regulations, UW Health providers:

- CANNOT bill for services provided to patients if those services are provided for by a study sponsor or grant. These include:
    - The investigational item or service, itself

  - Items and services provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan)
  - Items and services customarily provided, and paid by the research sponsors for any enrollee in the trial
- CAN bill for routine costs in Medicare Qualified Clinical Trials and for reasonable and necessary items and services used to diagnose and treat complications arising from the patient's participation in all clinical trials. Routine costs include:
  - Items or services that are typically provided absent a clinical trial (e.g., conventional care)
  - Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications
  - Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service--in particular, for the diagnosis or treatment of complications

The Research Billing Compliance Checklist provides more detail on what may and may not be billed for patients enrolled in a clinical trial.

Research Billing Compliance Program Website:
https://uconnect.wisc.edu/servlet/Satellite?pagename=B_EXTRANET_UWHC_DEPARTMENTS/Page/Show_Department&cid=1126670869715

Clinical Research Unit

The CRU, open 24/7, serves both inpatient and outpatient research studies on UWHC D6/6. Certified by the joint commission and supported by ICTR, the CRU has 19 research RNs, a nurse practitioner, a bionutritionist, and a sample processing laboratory. All RNs are Advanced Cardiac Life Support (ACLS) certified and chemotherapy-certified by UWHC. There is no nursing or room charge for federal and other investigator-initiated studies, but the PI must be an ICTR member and receive a CRU consult prior to IRB submission (https://ictr.wisc.edu/cru_consult). Industry studies are welcome, but pay UWHC for services at hospital rates.

Pharmaceutical Research Center

The PRC at the UWHC is responsible for the safe and ethical provision of study medications to subjects enrolled in clinical research studies at UW-Madison. **Regardless of the focus area of the study, all investigational drug studies conducted at UW require utilization of the PRC per hospital administrative policy**. PRC ensures that drug research protocols proceed optimally through the UWHC established medication use system and in accordance with all federal, state, institutional, and sponsor regulations governing clinical research.

PRC will review the protocol and conduct a feasibility assessment, evaluate budget impact, and determine study drug management requirements. PRC will work with the study team to outline workflow and expectations and will coordinate all aspects of study drug handling including receipt, storage, distribution, destruction, and accountability. PRC also plays an integral role in preparation of preprinted physician orders for study drug protocols.

The research team must provide advanced notification of pending protocols, as well as continual communication with PRC during the protocol activation process to ensure that activation date and other timeline expectations are met. PRC must also be notified in advance (two week minimum) of all pre-qualification visits, site initiation visits, and monitor/audit visits. This allows PRC to ensure appropriate staff are available for the appointment.

Research teams must provide PRC with all study-related documentation including information from the sponsor or coordinating center, and regulatory materials from the IRB of record (HS-IRB, WIRB, CIRB). A general rule is to copy PRC on all documents submitted to and received from the above entities to ensure PRC is compliant with regulatory requirements and is operating under the most current version of the protocol/procedures.

Because PRC utilizes the standard medication distribution system of the UWHC, research protocols may run twenty four hours per day, seven days per week. Office hours for the PRC are Monday through Friday from 7 am to 5 pm with continuous on call pharmacist coverage (via hospital pager 2717). For a timely response, PRC should be contacted via either the main telephone number, (608) 263-8863, or the group email address, rx-pharmaceuticalresearchcenter@hosp.wisc.edu.

Note: *PRC offers individual orientation sessions for new research staff to cover detailed information on PRC and the interface needed between research study staff and the service. Please contact PRC to schedule an appointment.*

UW Hospital and Clinics Lab Services

UWHC Clinical Laboratories strives to be a recognized leader in laboratory medicine by:

- Maintaining excellence in service to patients and health care providers, including physicians, nurses, and other health care professionals.
- Providing high quality and creative academic programs for health care professionals.
- Generating new knowledge to provide a foundation for meeting the health care needs of society.
- Promoting health care for the residents of the state of Wisconsin.

Laboratory Testing

Laboratory testing is performed 24 hours a day, seven days a week. The majority of tests are performed on site. Certain tests are referred to designated and approved reference laboratories.

Testing is performed by registered medical technologists and other trained professionals using the latest instrumentation. The rapid turnaround time provided by the laboratory allows caregivers in locations as diverse as the emergency department, intensive care units, and outpatient clinics to treat patients in a timely fashion. Members of the technical staff attend in-service training and continuing education programs on a regular basis to maintain and improve their laboratory skills.

Specimens for testing removed by biopsy or through surgery are examined by an expert staff of faculty pathologists, with specialties in hematopathology, renal pathology, cytopathology, and neuropathology.

Surgical Pathology:

The UWHC Surgical Pathology Laboratory receives tissue specimens from the operating rooms and clinics for consultation and diagnosis. Gross and microscopic examination, frozen section, and a variety of staining techniques are used in the diagnostic process. The laboratory also examines materials referred from other health service providers for initial diagnosis or consultation.

UWHC Policies 7.01 Pathology Specimen Care and Handling and **8.27 Requesting Consultations from Surgical Pathology Lab** describe the requirements for submission, identification, handling, and release of tissue specimens, including exemptions and guidelines for limited examination.

Research Radiology

The UW Radiology Research Program, housed in the Wisconsin Institutes for Medical Research Tower 2, provides comprehensive research services for the following imaging modalities: angiography; computerized tomography (CT); magnetic resonance imaging (MRI); positron emission tomography (PET); and ultrasound. Each modality has a clinical (MD) and technical director (PhD), research program manager, and one or more technologists. There are coordinators on the team, including nurses who oversee starting intraveneous drips and monitor AEs. The program also has a pre-award grants administrator who works with researchers to submit grants and contracts. The program also has a post-award grants administrator who works closely with a research accountant to proactively manage awards and closeout. In addition, the program has an IRB specialist who oversees regulatory compliance and a statistician who assists researchers with power calculations and analysis of the research imaging data.

For more information about policies related to the various imaging modalities and to submit an application, refer to the Department of Radiology research website (https://www.radiology.wisc.edu/research/scannerRequests/index).

UW ICTR Data Monitoring Committee

The ICTR Data Monitoring Committee (DMC) meets the requirements for an independent DSMC or a DSMB. The DMC is available for investigators when required by a funding agency, the PI, or IRB.

Co-chaired by Dave DeMets, PhD, and Norman Fost, MD, MPH, (September 2014), the DMC meets monthly and is comprised of experienced clinical researchers from diverse backgrounds and skill sets. The DMC helps investigators ensure subject safety, research integrity, and compliance with federal regulations and local policies. The DMC also makes recommendations to the PI that could include actions of continuation, modification, or termination.

For more information, visit https://www.ictr.wisc.edu/DMC.

Office of Clinical Trials

The mission of the Office of Clinical Trials (OCT) is to support the clinical research activities of SMPH investigators and others by providing high quality clinical research support in all aspects of trial development and management. OCT performs comprehensive feasibility assessments to help potential investigators determine whether the considered project is financially and practically feasible, and provides them with specific information to help reach a decision about participation.

OCT also provides a venue to connect industry sponsors with potential investigators when specific industry-sponsored protocols are looking for investigative sites.

Regulatory and fiscal services include:

- Confidential disclosure agreements
- Research budget preparation and negotiation
- Marginal budgeting estimates and ongoing invoicing/ reconciliation services
- Contract routing and completion
- Preparation of regulatory submissions for WIRB, VA, and HS-IRB
- Research coordination services from initial study development to final monitoring.
- UW guidance for use of Clinicaltrials.gov
- Grant budgeting estimates

OCT research coordinators are available to assist with aspects of study data collection that do not require licensure, such as recruitment, obtaining informed consent, and data collection. They are capable of managing all aspects of study initiation including order and document development. They conduct subject research visits and carry out or facilitate all study assessments. In addition, a specialized team of OCT coordinators is available for 24/7 response to off-hours protocol visits and consenting opportunities.

For more information, contact: ctrials@clinicaltrials.wisc.edu *or visit* https://ictr.wisc.edu/OCT.

Department of Dermatology

The UW Department of Dermatology provides adult and pediatric clinical services at a number of outpatient locations in Madison, as well as in the transplant and melanoma clinics located in the UWHC, including the AFCH. The Department of Dermatology faculty offer subspecialty care in

pediatric dermatology, Mohs and dermatologic surgery, Psychocutaneous medicine, and comprehensive dermatopathology services including immunoperoxidase and molecular diagnostics.

The Department of Dermatology provides innovative research programs in both clinical and basic science to address a variety of problems focusing on targets and agents for cancer chemoprevention and treatment, molecular mechanisms of cancer development, molecular diagnosis of skin diseases, studies testing novel treatments, and translational research investigating genetic correction of skin diseases. Through the Skin Diseases Research Center, the program offers funding for pilot and feasibility studies from young investigators, established dermatologic investigators embarking on new topics, and other established investigators entering skin diseases research. In addition, the program collaborates with investigators from other disciplines or specialties to provide dermatology support as dictated by clinical protocols, such as allergy testing.

Refer to the Department of Dermatology research program website for more information (http://www.dermatology.wisc.edu/research.htm).

Division of Cardiovascular Medicine

The Division of Cardiovascular Medicine in the UW Department of Medicine conducts many single and multi-center clinical research trials sponsored by the NIH, philanthropic organizations, and industry.

Since this clinical research program was initiated in 1984, numerous clinical protocols have involved patient volunteers in studies of promising new therapeutic agents and devices. Patients participating in clinical research protocols develop very special relationships with study personnel, and appreciate the unusually thorough attention to detail and the inherent ongoing educational opportunities. Faculty, trainees and nurses have the opportunity to participate in developing new knowledge and contributing to evidence-based medical care.

In addition to conducting their own clinical research studies, the Division offers various clinical services to researchers, including:

- Electrocardiogram
- Echocardiogram
- Exercise Stress Testing
- 24-48 hour rhythm monitoring
- 30 day event monitoring

For more information, visit their website at (http://www.medicine.wisc.edu/cardiology/researchinto).

Services offered to UW-Madison clinical researchers:

- Non-Invasive - ECG and Stress Testing
- Non-Invasive - Echocardiograms and Vascular Testing
- Invasive Cardiology (catheterization)

Ophthalmology Clinical Trials Unit

The UW Ophthalmology Clinical Trials Unit has conducted human subjects research for over 25 years. While the original mission of the office was to administer research projects related to age-related macular degeneration (AMD); current roles, responsibilities and areas of expertise have expanded to include trials related to diabetic macular edema, diabetic retinopathy, retinal vein occlusion, ocular melanoma, glaucoma, and pediatric ophthalmic diseases. These trials are designed to evaluate the safety and efficacy of new laser treatments, oral medications, IV medications, intravitreal injections, surgeries, vitamins, minerals and devices in the treatment of ophthalmic diseases.

In addition to managing their own ophthalmic trials, they also collaborate with many other UW-Madison departments to conduct the ophthalmology procedures necessary when studying new medications that could have risks associated with damage to the eye. Such procedures include: visual acuity (ETDRS visual acuity), eye pressure (tension check), slit lamp exam, bilateral ocular exam (dilated exam), fundus photos, fluorescein angiography, optical coherence tomographyscans, electroretinography, Humphrey visual field, color testing, reading speed, and contrast sensitivity testing.

The Ophthalmology clinical coordinators are trained, medically-qualified personnel with sufficient expertise, training, and experience to comply with GCP and the requirements of the study protocols. The Ophthalmology coordinators work closely with other members of the research team to schedule subjects for their ophthalmic procedures in the study, and also work closely with subjects to collect required data in a timely manner.

To learn more, or consult with the Ophthalmology Clinical Trials Unit, visit their website (http://www.ophth.wisc.edu/research/).

B. Health Services Research, Population Health Research & Dissemination Programs

Collaborative Center for Health Equity

The ICTR Collaborative Center for Health Equity has relationships with tribal, urban, and rural partners in Wisconsin, in addition to state and local government collaborations. Their approach allows creation of long-term, mutually respectful, and trusting partnerships with underserved communities.

Health Innovation Program

The Health Innovation Program supports health services research projects in collaboration with local and statewide health systems. Such projects include research on the quality and cost of health care and research to examine the impact of improvement interventions over time. Extensive resources are available that support the use of electronic health records and Medicare or other health care claims data for research purposes.

Health Policy Group

The Health Policy Group provides policymakers, in both the public and private sectors, with timely, nonpartisan, high-quality information for evidence-based policy decision-making and works to increase the involvement of UW faculty research and teaching activities in topical issues of state public policy.

Marshfield Clinic Center for Clinical Epidemiology and Population Health

ICTR Community-Academic Partnerships core at Marshfield Clinic Research Foundation, housed within the Marshfield Clinic Center for Clinical Epidemiology and Population Health, supports development and collaboration in funded population research. The core facilitates access to several defined patient population cohorts, and also fosters interaction of Marshfield Clinic in the local area to support community engagement and community-engaged research. This resource specializes in effectiveness and patient-centered research, research into optimal dissemination and implementation strategies, and formal dissemination and implementation of relevant findings to appropriate stakeholder groups.

ICTR Qualitative and Mixed Methods Research Resource

ICTR Qualitative and Mixed Methods Research Resource can offer support to investigators whose research design incorporates qualitative or mixed methods.

UW School of Engineering-based Simulation Center

The UW School of Engineering-based Simulation Center supports research that strives to estimate the potential impact of type 2 translational research using modeling and simulation, by developing quantitative decision-analytical models to optimize medical decision making and by using mathematical/computer models for policy formation in health care.

Sonderegger Research Center

The UW School of Pharmacy-based Sonderegger Research Center supports the organization, delivery, financing, quality and outcomes of pharmacy within the broader health care system, as well as characterizing patient-provider interactions including access to videotaping capacity and support.

Systems Engineering Initiative for Patient Safety

UW Systems Engineering Initiative for Patient Safety supports patient safety research that integrates human factors engineering (design, development and deployment of systems), healthcare systems, and health information technology.

VA Hospital Research Program

William S. Middleton Memorial Veterans Hospital Research Program supports research directed at the health and care needs of veterans, including but not limited to, aging-related conditions, mental health care and well-being, chronic disease, long-term care and caregiving, deployment-related exposure to hazardous environmental agents, equity and access, women's health, and personalized medicine.

Wisconsin Network for Research Support

The Wisconsin Network for Research Support offers consultation and training services to help investigators develop materials that are accessible and engaging for target populations. WINRS staff also coordinates meetings with Community Advisors on Research Design and Strategies focus groups of community members from diverse racial, ethnic, socioeconomic, and educational backgrounds who are trained to give feedback to investigators on recruitment plans and materials, consent forms, and survey or interview questions.

Wisconsin Surgical Outcomes Research Group

The Wisconsin Surgical Outcomes Research Group mission is to improve the quality, safety, effectiveness and efficiency of surgical care through research and innovation. This group provides an intellectual home for surgical outcomes research while providing support and resources to facilitate and expedite research. They are also committed to career development and training for the next generation of researchers pursuing health services research in the field of surgery.

C. Practice Based Research Networks

Community-Academic Aging Research Network

Community-Academic Aging Research Network aims to augment the capacity and effectiveness of both Wisconsin's aging services network and the UW to conduct clinical and dissemination research related to aging.

Pharmacy Practice Enhancement and Action Research Link

Pharmacy Practice Enhancement and Action Research Link is a statewide research network of over 60 community, clinic, and hospital pharmacists with the goal of building capacity for practice-based research initiatives in response to opportunities that can enhance and advance pharmacy practice in the state.

Wisconsin Public Health Practice-Based Research Network

Wisconsin Public Health Practice-Based Research Network is working to develop a practice-based research network in Wisconsin that will focus on public health systems and services.

Wisconsin Research & Education Network

The Wisconsin Research & Education Network is a statewide primary care, practice-based research network. Researchers may collaborate with the network when their research involves partnerships with multi-site primary care clinicians, practices, and the communities they serve; quality improvement/enhancement; and underserved populations.

Wisconsin Network for Health Research

Wisconsin Network for Health Research (WiNHR) is a collaborative research consortium nested within ICTR that provides a venue for researchers to conduct clinical, translational, comparative effectiveness, and health outcomes research at multiple health-care institutions across the state of Wisconsin. WiNHR partners include the UW SMPH, Marshfield Clinic Research Foundation, Aurora Health Care, and Gundersen Health System. WiNHR was originally established in 2005 with the goal of improving health across the state; enhancing the ability of researchers to evaluate new health care interventions; establishing new or improved collaborative research relationships among medical centers throughout the state; and increasing cross-discipline exploration and discovery.

WiNHR provides researchers and extramural sponsors with 1) a statewide geographic reach that includes patient populations from urban, rural, and ethnically diverse communities; 2) access to more than 5.2 million Wisconsin residents in 52 counties; 3) specialty and primary care collaborators from WiNHR partner institutions; 4) increased efficiency in conducting research and meeting accrual goals; and 5) established infrastructure at network sites such as standardization of operating procedures, reciprocal protocol deferral through the Wisconsin IRB consortium, and multisite study data management using OnCore® software.

Midwest Area Research Consortium for Health

Midwest Area Research Consortium for Health (MARCH) was founded in 2012 to transform the research enterprise by enhancing the efficiency and quality of clinical research, accelerating the

process of translating laboratory discoveries into treatments for patients, and engaging in national collaborations to synergize and catalyze multisite research opportunities at NIH Clinical and Translational Science Award sites. Founding MARCH members include Indiana University, Mayo Clinic, Medical College of Wisconsin, The Ohio State University, University of Minnesota, and University of Wisconsin.

The mission of MARCH is to improve health through collaborative multidisciplinary clinical research and integration of evidence into clinical practice. MARCH provides researchers and extramural sponsors with: 1) collaborative clinical research partnerships at academic institutions across the Midwest; 2) inter-institutional exchange of best practices in research; 3) shared resources available for collaborative and efficient regulatory and fiscal processes, thereby minimizing duplication; 4) standardized data management and reporting through clinical trial management systems; 5) established standard operating procedures for assurances of quality; 6) a centralized model for effective administration and coordination mechanisms; and 7) the capacity to effectively perform studies in rare diseases and in populations that are very large and/or of varied demography.

References:

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report -- Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Washington, DC: U.S. Department of Health and Human Services: Part C, section 2, “Assessment of risks and benefits” http://ohsr.od.nih.gov/guidelines/belmont.html

Respect for Persons, p 3 *Informed Consent*. Emanuel, EJ et al., eds. 2003. Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary. Baltimore, MD: The Johns Hopkins University Press, p.189.]

Appelbaum PS1, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. IRB. 2004 Mar-Apr;26(2):1-8.

Hazra, A. Use, abuse and miuse of notes to file. Perspect Clin Res. 2011 Jan-Mar; 2(1): 38–40.’ in the bibliography. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3088955/

Website links included in this manual:

NIH Glossary & Acronym List: http://grants.nih.gov/grants/glossary.htm

ClinicalTrials.gov Glossary: https://clinicaltrials.gov/ct2/about-studies/glossary

FDA Glossary (Drugs): http://www.fda.gov/drugs/informationondrugs/ucm079436.htm

The full DHHS organizational chart: http://www.hhs.gov/about/orgchart/

UW-Madison Health Sciences IRB Website: https://kb.wisc.edu/hsirbs/

UW-Madison Education/Social & Behavioral Sceinces IRB Website: http://www.irb.wisc.edu/

UW Institute for Clinical and Translational Research: https://ictr.wisc.edu

UW ICTR Clinical Research Toolkit: https://ictr.wisc.edu/clinical-research-toolkit/

UW-Madison Office of Research Policy: http://grad.wisc.edu/respolcomp/

UW Health Internal Webpage: https://uconnect.wisc.edu

School of Medicine and Public Health Intranet: http://intranet.med.wisc.edu/policies-and-procedures/main/30845

UW-Madison, Division of Business Services, Accounting Services: http://www.bussvc.wisc.edu/acct/policy/pir/pirpol.html

Office of Research and Sponsored Programs: https://www.rsp.wisc.edu/

FDA Guidance on Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf

The Belmont Report: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

NIH Data Safety Monitoring Plan requirements: http://www.nlm.nih.gov/ep/dsm.html

OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: http://www.hhs.gov/ohrp/policy/advevntguid.html

NIH Policy for Data and Safety Monitoring : http://grants.nih.gov/grants/guide/notice-files/not98-084.html

NIH Requirements for Data Safety and Monitoring Plans: http://www.nlm.nih.gov/ep/dsm.html

NIH: Further Guidance on Data and Safety Monitoring for Phase I and Phase II studies: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

FDA Guidance Documents: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127073.pdf

Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs - Improving Human Subject Protection, January 2009: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126572.pdf

Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, August 2013: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

FDA Code of Federal Regulations: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

International Conference on Harmonization Good Clinical Practice: ichgcp.net

UW-Madison Best Practices for Record Keeping: http://archives.library.wisc.edu/records/trainmats/2012_12_Basic_University_Records%20-%20for%20hand%20out.pdf

UW-Madison Research Records: http://archives.library.wisc.edu/records/trainmats/2013%20Research.pdf

UW-Madison Records Management toolkit: http://archives.library.wisc.edu/records/resource.html#bulletins

OHRP Tips on Informed Cosnent: (http://www.hhs.gov/ohrp/policy/ictips.html

DRAFT Guidance for IRBs, Clinical Investigators and Sponsors: Informed Consent Information Sheet: http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm

NIH Certificate of Confidentiality: http://grants.nih.gov/grants/policy/coc/index.htm

UW-Madison Health Information Portability & Accontability Act (HIPAA) Website: http://www.hipaa.wisc.edu/

Safety Profiler/Common Terminology Criteria for Adverse Events (CTCAE) maintained by the NCI: http://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx

FDA Guidance on Safety Reporting for INDs and BA/BE Studies http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm227351.pdf

September 2013 FDA guidance titled “Electronic Source Data in Clinical Investigations”, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf

UW-Madison Environment, Health and Safety Department: Hazmat Training:http://www.ehs.wisc.edu/hazmatshipping.htm

UWHealth Research Billing Compliance Program: https://uconnect.wisc.edu/servlet/Satellite?pagename=B_EXTRANET_UWHC_DEPARTMENTS/Page/Show_Department&cid=1126670869715