UT Southwestern Medical Center

Clinical Research Handbook

A Guide to Conducting Clinical Research at UT Southwestern Medical Center

Acknowledgements

This handbook contains information that introduces clinical researchers to the concepts and skills necessary to be successful in their role. This resource could not have been completed without the assistance and oversight from numerous individuals across many disciplines and institutions at UT Southwestern Medical Center and affiliates.

We would like to acknowledge all the members of the UT Southwestern Clinical and Translational Science Award (CTSA) Program as well as the Office of Clinical Research (OCR), and Human Research Protection Program (HRPP) who contributed significantly to the development and review of this handbook.

The handbook also includes contributions from representatives within a variety of disciplines, departments, programs and roles in clinical research, as well as UT Southwestern's affiliated hospitals:

- Sponsored Programs Administration (SPA)
- UTSW Simmons Comprehensive Cancer Center (SCCC)
- Office of Research Support and Regulatory Management (RSRM)
- Children's Health
- Parkland Health
- Scottish Rite for Children
- Texas Health Resources

…among many others.

Finally, we would also like to extend a sincere thank you to all involved in creating content for the Clinical Research Foundations course, and offering feedback, suggestions for improvement, and assistance.

We are excited to begin a new phase in clinical research education at UT Southwestern Medical Center, which will set the standard for all incoming researchers to quickly learn the fundamentals for conducting research.

Please do not hesitate to reach out to OCR@utsouthwestern.edu if you have any questions.

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Disclaimer

This initial Clinical Research Handbook is an ongoing project. All efforts have been made to present the most up-to-date information available. However, if you see any areas that require updates, please contact us at OCR@UTSouthwestern.edu.

Document Information:

Version	Published online	Reason for updates
1.0	07Jul2023	N/A
1.1	12Dec2023	• In Chapter 2: In the section under the Conflict of Interest (COI) and Institutional COI (ICOI) Committees, update the sections with clarifying language. (Pages 61-62, 67-68) • In Chapter 2: In the section under the Regulatory Support Office (RSO), add another bullet point under responsibilities: "FDA submissions for Expanded access/ single patient use." (Page 46) Fix the civil monetary penalties listed for failure to comply with ClinicalTrials.gov Reporting. The amount was previously listed as a fee of **$3,237** per day, when it should be **$13,237** per day. Clarify RSO's role in the ClinicalTrials.gov Reporting Support Program. (Page 48) Clarify when FDA registration should occur. (Page 157) Insert additional information into the FAQ section for the RSO. (Page 256) • In Chapter 2: Update the reference to other entities from Section I to Section J. (Page 83) Update the Office of Technology Development (OTD)'s section with minor clarifying language. (Page 85) • In Chapter 7: Update the Informed Consent section to insert the HRPP's website link to their Policies and Procedures page. (Page 160) • In Chapter 7: Update the instructions for using the Priority for Consent Purposes. (Page 178) • In Chapter 11: Under the FAQ section the OCTM updated their virtual office hours information (Page 254) • Minor formatting updates (e.g., align margins, align bullet points, standardize font sizes) throughout the document • Fix minor misspellings (e.g., da-a printed instead of data) throughout the document

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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

ACTs	Applicable Clinical Trials
ADL	Activities of Daily Living (type of questionnaire)
AE	Adverse Event
AFCH	American Family Children's Hospital
AHC	Academic Health Center
AIRC	Advanced Imaging Research Center
APRegN	Advanced Practice Registered Nurse
APRsN	Advanced Practice Research Nurse
ASD	Autism spectrum disorder
BA/BE	Bioavailability/Bioequivalence
BERD	Biostatistics, Epidemiology, and Research Design Clinic
BLA	Biologic License Application
BMI	Body Mass Index
CA	Coverage Analysis
CAP	College of American Pathologists (lab accreditation)
CAPA	Corrective and Preventive Action
CBER	Center for Biologics Evaluation and Research
CCAG	Central Coverage Analysis Group
CDA	Confidential Disclosure Agreement
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health (FDA)
CFR	Code of Federal Regulations
CHS	Clinical/Health Sciences
CIO	Chief Information Officer
CIRB	National Cancer Institute (NCI) Central Institutional Review Board (NCI CIRB)
CLIA	Clinical Laboratory Improvement Amendments (lab certification)
CLS	Clinical Laboratory Services
CLSR	Clinical Laboratory Services Research

CMPA	Office of Communications, Marketing, and Public Affairs
CMS	Centers for Medicare & Medicaid Services
COA	Chart of Account
CoC	Certificate of Confidentiality
COC	Conflict of Commitment
COI	Conflict of Interest
CRC	Clinical Research Coordinator
CRCO	Clinical Research Compliance Office
CRF	Case Report Form
CRM	Clinical Research Manager
CRO	Clinical Research Office
CROrg	Clinical Research Organization
CRU	Clinical Research Unit
CSC	Chemical Safety Committee
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
DADMC	Diminished Autonomous Decision-Making Capacity
DFS	Disease-free survival
DG	Dangerous Goods
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DMS	Data Management and Sharing
DOA	Delegation of Authority
DOD	Department of Defense
DOE	Department of Energy
DoT	Department of Transportation
DOT	Disease-Oriented Team (in the SCCC)
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
DTA	Data Transfer Agreement
DUA	Data Use Agreement
EC	Export Control

ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
ED/SBS	Education Research/Social and Behavioral Sciences IRB
EDC	Electronic Data Capture
eIRB	electronic Institutional Review Board
EKG	Elektrokardiogram (German spelling of ECG)
FDA	Food and Drug Administration
FISMA	Federal Information Security Management Act
FUA	Facility Use Agreement
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
HDE	Humanitarian Device Exemption
hESCs	Human Embryonic Stem Cells
HIPAA	Health Insurance Portability and Accountability Act
HM	Hazardous Materials
HMRIC	Human MRI Core (part of AIRC)
HRPP	Human Research Protection Program
HS IRB	Health Sciences Institutional Review Board
HUD	Humanitarian Use Device
IA	Internal Audit
IACUC	Institutional Animal Care and Use Committee
IATA	International Air Transport Association
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICAO	International Civil Aviation Organization
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
ICOI	Institutional Conflict of Interest
IDB	Investigational Drug Brochure
IDE	Investigational Device Exemption
IDS	Investigational Drug Services (Pharmacy)
IIT	Investigator Initiated Trials
IND	Investigational New Drug

IO	Institutional Official
IP	Investigational Product
iPSCs	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IRT	Investigator Relations Team
IT	Information Technology
ISAC	Information Systems Acquisition Committee
LAR	Legally Authorized Representative
LDS	Limited Data Set
LOI	Letter of Intent
MOP	Manual of Procedures
MR IRB	Minimal Risk Institutional Review Board
MRI	Magnetic Resonance Imaging
MRN	Medical Record Number
MTA	Material Transfer Agreement
MUGA	Multiple-gated acquisition scan
NCI	National Cancer Institute
NCT	National Clinical Trial number (used on ClinicalTrials.gov)
NDA	New Drug Application
NIH	National Institutes of Health
NP	Nurse Practitioner
NPP	Notice of Privacy Practices
NSF	National Science Foundation
NSR	Non-significant risk
NTF	Note to File
NYHA	New York Heart Association
OAR	Outside Activities Report
OCHRE	Office of Community Health and Research Engagement
OCR	Office of Clinical Research
OCTM	Office of Clinical Trial Management
OHRP	Office for Human Research Protection
OS	Overall Survival
OSBC	Office of Safety and Business Continuity
OTC	Over the counter
OTD	Office for Technology Development
PA	Physician Assistant

PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PMA	PreMarket Approval
PMS	Payment Management System
PMS	Post-Marketing Surveillance
POI	Person of Interest
PRC	Pharmaceutical Research Center
PRMC	Protocol Review Monitoring Committee
PRMS	Protocol Review and Monitoring System
PRS	Protocol Registration and Results System
PS	Performance Site
PSRF	Performance Site Review Form
PSSV	Pre-Site Selection Visit
QA	Quality Assurance
QAM	Quality Assurance and Monitoring
QAR	Quality Assurance Review
QoL	Quality-of-Life (type of questionnaire)
QC	Quality Control
RA	Regulatory Analyst
RAS	Research Academic Systems
RBR	Research Billing Review
RCR	Responsible Conduct of Research
RDRC	Radioactive Drug Research Committee
RE	Reportable Event
RN	Registered Nurse
RR	Response Review
RS	Regulatory Specialist
RSAC	Radiation Safety Advisory Committee
RSC	Research Safety Committee
RSO	Regulatory Support Office
RSP	Research and Sponsored Programs
RSRM	Research Support & Regulatory Management
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center

SCRO	Stem Cell Research Oversight
SHUR	Subcommittee for Human Use of Radiation in Research
sIRB	Single Institutional Review Board
SIV	Site Initiation Visit
SMoR	Study Monitor of Record
SMPH	School of Medicine and Public Health
SMS	Study Monitoring Service
SOA	Service Order Agreement
SOP	Standard Operating Procedure
SOW	Scope/Statement of Work
SPA	Sponsored Programs Administration
SQV	Site Qualification Visit
SSV	Site Selection Visit
Sub-I	Sub-Investigator
TACE	Transcatheter arterial chemoembolization
TPIA	Texas Public Information Act
UADE	Unanticipated adverse device effects
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others
UPS	Unanticipated Problems
VA	Veterans Affairs
WIRB	Western Institutional Review Board (a type of central IRB)

Introduction

The purpose of this handbook 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 UT Southwestern.

This handbook is intended to accompany and complement the UT Southwestern curriculum, which includes the CITI course and video productions, and to serve as a resource and reference for our research staff. This handbook has been written both as an introduction to best practices for those who are new to clinical research at UT Southwestern, and as a refresher for more experienced clinical research staff.

The content in this handbook is geared toward research staff who oversee the management of clinical research studies within the UTSW environment. However, the majority of the 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 handbook, 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 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 handbook, the terms **clinical research study** and **clinical trial** will be used interchangeably.

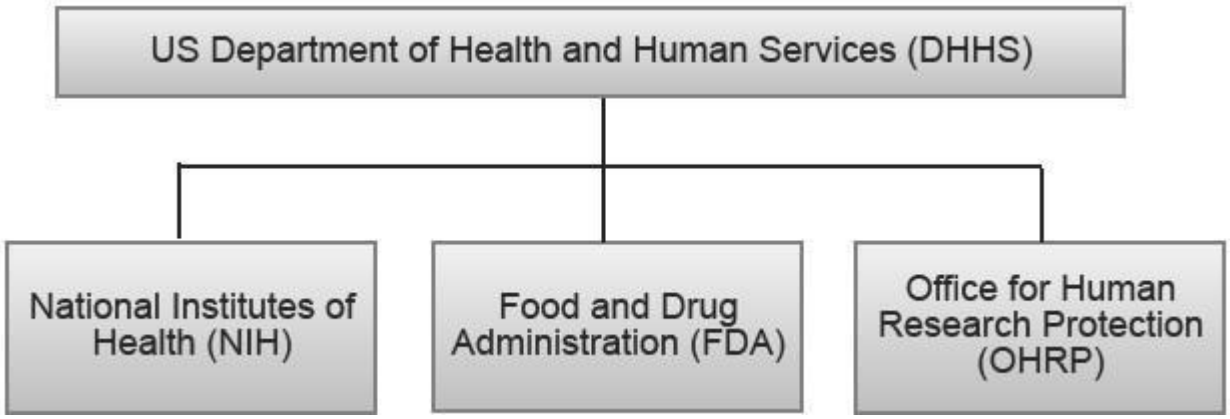
Chapter 1: Basic Concepts in Clinical Research

A. Overview of Clinical Research Regulations and Guidance

Depending on the research study type and the specific funding agency or sponsor, multiple levels of regulatory and compliance oversight may be involved, including federal regulations, state laws, institutional policies and guidelines, and funding agency or sponsor policies and guidelines. Even if you are not able to fully understand all the complex regulations and policies, it is important to be aware of their presence and impact on clinical research operations as they all contribute to the **foundation** for and direct 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 Code of Federal Regulations (CFR) is the codification of the general and permanent rules

published in the Federal Register by the executive departments and agencies of the Federal Government. The CFR has 50 titles representing broad areas subject to Federal regulation. 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)

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 US Department of Health and Human Services (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 UT Southwestern, 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. In fact, NIH is the largest public funder of biomedical and behavioral research in the world. NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

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 all human subjects research if it involves drugs, devices, biologics and/or vaccines. These types of studies must adhere to CFR Title 21.

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

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.

According to the FDA, an **investigational drug** is the object of clinical investigations to determine the **safety and effectiveness** of the drug. The term **investigational drug** in this handbook 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 handbook.

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.

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.

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 as if reviewing an investigational new drug application (IND) application.

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.

B. Federalwide Assurance

For an institution to accept federal research funding, it must obtain, or hold, a **Federalwide Assurance (FWA)**. The FWA is effective for 5 years and must be renewed by the institution every 5 years, even if no changes have occurred, in order to maintain an active FWA. Any renewal or update that is submitted electronically, and approved by OHRP, begins a new 5-year effective period. UT Southwestern's FWA provides assurance to the federal government that all investigators working on human subjects research will comply with the **terms of assurance**.

Other institutions covered by the UT Southwestern's FWA include the following:

- Parkland Health and Hospital System
- Scottish Rite for Children
- Children's Health
- Texas Health Resources

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 UTSW or other UT Southwestern clinical research environments.

UTSW is comprised of The University of Texas Southwestern Medical Center, inclusive of the Graduate School of Biomedical Sciences, Medical School, School of Allied Health Sciences, UT Southwestern Moncrief Cancer Center, Zale Lipshy University Hospital, and William P. Clements Jr. University Hospital, and other centers and organized research units within UT Southwestern Medical Center.

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 handbook 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, UT Southwestern typically participates as one of a number of study sites.

A clinical research organization (CROrg) may be contracted by the sponsor to manage some or most of the tasks related to study conduct and management, such as regulatory affairs, clinical trial planning, site selection and initiation, recruitment support, clinical monitoring, data management, trial logistics, biostatistics, medical writing, and project management. To provide oversight, a CROrg often sends a monitor to a study site to review study records and data, although monitoring can also be done remotely. The monitor will also submit reports to the sponsor regarding the site's conduct on the study, as well as meet with the Principal Investigator periodically to report on the team's ongoing performance. By reviewing the study team's work and providing timely feedback, the monitor ensures that the information recorded by the study team is both accurate and up-to-date, both of which have a significant impact on the scientific validity of the study.

Sponsor-Investigator

A **sponsor-investigator** is an individual who both **initiates and investigates**. 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)

Studies managed under a sponsor-investigator are referred to as *Investigator-Initiated*. The obligations of a **sponsor- investigator** include both those of a sponsor as well as those of a principal investigator.

The investigator often seeks funding or support for the aforementioned studies from non-profit organizations, foundations, private funding, departmental or institutional funding, and/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 becomes most apparent that a PI is acting as 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 each of the various federal agencies referenced above there are also numerous subdivisions. For example, the NIH has 27 institutes and centers that support research whose funding falls within the federally-sponsored category (NIH Organization | National Institutes of Health (NIH)). Some examples of those institutes and centers include 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), just to name a few. The various centers and institutes may also 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. Depending on the study, 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 chronic illnesses. Supportive care research may involve drugs, nutritional, behavioral, or psychosocial interventions. It's important to note that supportive care research is intended to help the patient achieve comfort but does not affect the ultimate course of a disease.

Non-Intervention

There are types of studies that do not 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. In the most basic of terms, epidemiology is the study of the frequency with which diseases and/or disorders affect different groups of people and the reasons why they occur. Epidemiologic studies, also known as observational or outcomes studies, can involve healthy populations as well as diagnosed patients. Epidemiological research helps us to understand how many people suffer from a disease or disorder, if those numbers are changing, and how the disorder affects our society and our economy. These studies often include observation or surveillance, surveys, outcomes, or monitoring the subject's environment.

An interesting facet of studying disorders is that the accepted definition of a disorder also tends to change over time as new information from scientific research becomes known, making the aspect of researching the disease or disorder continuously challenging. For example, even scientists working in the same field at the same time may not always agree on the best way to measure or define a particular disorder. What may be assumed as the incidence (i.e., the number of new cases within a defined time) of a disorder within a larger

population may change as new awareness regarding that disorder emerges. The rise in autism spectrum disorder (ASD) in the United States is an example of increased incidence most likely due to a general growing awareness of autism and changes to the condition's diagnostic criteria.

Chart Review

Chart review studies collect data from patient medical records. A chart review study could be retrospective, prospective, or both. Chart reviews are a common research method of gathering data on a specific medical condition or set of patient characteristics. For instance, a typical chart review study would be one that collects information from hospital 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. These are also often referred to as databanks, or data registries. A registry is a collection of information about individuals, usually focused on a specific diagnosis or condition, although the research question may not yet be known. The data to be collected needs to be identified. This identifiable information is protected by law under strict privacy agreements, such as the Federal Information Security Management Act (FISMA), and the Health Insurance Portability and Accountability Act (HIPAA).

Many registries collect information about people who have a specific disease or condition, while others seek participants of varying health status who may be willing to participate in research about a particular disease. Individuals provide information about themselves to these registries on a voluntary basis. Registries can be sponsored by a government agency, nonprofit organization, health care facility, or private company. Examples of registries include the Cutaneous Lupus Registry, Morphea Registry, Biorepository and Patient Registry, ConTex Registry, Orthopedic Hip Registry, COVID Registry, Concussion Registry, Be the Match Registry, INTERMACS Registry, among others.

Biospecimen Repository

Biospecimen studies involve collection of biological specimens from healthy volunteers and/or diagnosed patients. These are also often referred to as biobanks, or specimen banks. The specimens may be used in ongoing laboratory studies or may be preserved for future

use. Moreover, the repository locations may be external (i.e., housed off campus, such as with the study's sponsor) or local (i.e., stored on UT Southwestern's campus in a controlled environment).

Human biospecimens include–but are not limited to–blood and other body fluids, tissues, and other biological materials obtained from humans. Per UT Southwestern's policy RES-155 Biorepository Oversight Committee – Handbook Policy (compliance360.com), biospecimens are defined as, "human biological materials including but not limited to tissue, organs, blood, plasma, serum, CSF, DNA, proteins, and all other materials derived from human subjects." Subsets of human materials, such as derived cell lines that are traceable to a human subject or patients with linked identifiers or Personally Identifiable Information (PII) as well as those materials that cannot be linked to identifiers, should also be handled as independent biospecimens per the NIH. A list of biospecimens recognized by the NIH are included in this document: https://oir.nih.gov/system/files/media/file/2021-11/guidelines-biospecimen.pdf.

Biorepository

Finally, another non-intervention study category recognized at UT Southwestern are biorepositories, which contain both data as well as biospecimens specimens. Per UT Southwestern's policy RES-155 Biorepository Oversight Committee – Handbook Policy (compliance360.com), biorepository is defined as, "a storage site for biospecimens where the biospecimens are collected from various sources and stored or archived to support current or future scientific investigation."

Under the definition of human subject at 45 CFR 46.102(f), obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining identifiable private information or identifiable specimens includes, but is not limited to:

- using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to investigators from any source; and
- using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were already in the possession of the investigator.

In general, OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the

investigator(s) either directly or indirectly through coding systems.

For additional guidance on UT Southwestern's policy on repositories, please review policy_2.9repository.pdf (utsouthwestern.edu). If you have any other questions regarding the non-intervention study types and topics listed above, please reach out to the HRPP: Human Research Protection Program (HRPP): UT Southwestern, Dallas, Texas.

Although not required, UT Southwestern encourages teams to consider using an honest broker to assist with maintaining the privacy of the identifiable private information within their dataset, biorepository, etc. An honest broker can essentially create a firewall between the investigator and the subjects' identifiable information needed for the study. For example, an honest broker could generate or receive a dataset and then strip out all of the subject identifiers so that the data is no longer readily identifiable by anyone on the study team. They can create a de-identified data set or a limited data set (LDS), which would then be turned over to the study team to utilize for their research. There are different types of honest brokers that can be involved in clinical research, depending on what the study requires.

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 is extended for a longer period of time than what was offered in the initial study. Extension studies are considered a new protocol, even if they are designed exactly the same as the initial study (e.g., same treatment parameters and schedule of activities). The difference in the extension studies is usually due to the different enrollment procedures. Only those subjects who participated 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. Post-Trial Access (PTA) refers to the provision of a product to research participants following study completion. PTA may involve open-label trial extension studies, long-term extension studies, rollover clinical

studies, separate protocols, or protocol amendments.

Scientific or Sub-study (Ancillary)

Scientific, or sub-studies, sometimes referred to as ancillary studies, involve procedures done in addition to the main study to answer additional questions. A sub-study poses a separate research question than the parent protocol, contributes to the parent protocol's objectives, and uses all or a subset of the participant information or specimens collected during the main study. For example, an investigational drug study may also collect laboratory samples from the study's enrolled subjects to analyze the effects of the investigational drug on a certain protein. The purpose of the main study is to evaluate the safety and effectiveness of the investigational drug, while the scientific or sub-study collects information about the protein.

These scientific/sub-studies may be designed to be optional or required for the subject to participate in the main study. In addition, they may either be embedded in the main study, or they may be a separate stand-alone study, requiring a separate protocol and perhaps a separate consent form.

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

Correlative

Correlative research examines the statistical relationship between two or more variables without manipulating them. It is considered non-experimental since it only seeks to establish the degree of association or correlation between two or more variables to determine the type of correlation: positive (two variables increase or decrease together), negative (one variable increases while the other decreases), or zero (there is no relationship between two variables). This type of research design is often applied to laboratory, or radiology-based, studies that utilize subject specimens to identify assessment of risk, clinical outcomes, and/or therapy response. For example, researchers may use correlational research to analyze the potential relationship between unhealthy behaviors, such as smoking, and the incidence prevalence (the number of existing cases of a disease in a population at a given time) of lung cancer.

Adjuvant Treatment Studies

Adjuvant studies offer 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. In other words, even if a patient's surgery to remove a cancerous tumor is considered successful at removing all visible cancer, microscopic bits of cancer sometimes remain and are often undetectable with current imaging technology and methods. Types of adjuvant treatments typically offered in these studies include chemotherapy (using cancer killing drugs), hormone therapy (to stop hormone production in your body or block the effect of hormones), radiation therapy (high-powered energy beams, such as X-rays or protons, to kill cancer cells and given internally or externally), immunotherapy (which stimulates your body's own immune defenses or supplements them), and targeted therapy (designed to alter specific abnormalities present within cancer cells. For example, a targeted therapy is available to block the action of a protein called human epidermal growth factor receptor 2 (HER2) in women with breast cancer). Adjuvant treatment studies can offer a variety of additional treatment options that may further decrease the chance of the cancer coming back, also known as cancer recurrence.

Neoadjuvant Treatment Studies

Neoadjuvant studies provide additional therapies (e.g., chemotherapy, radiation therapy, and hormone therapy) before standard treatment, which is usually surgery. Such studies evaluate treatments designed to reduce tumor size to a point where it can be effectively treated by standard-of-care therapies. Within clinical research, true neoadjuvant studies test the administration of a new drug or regimen preoperatively, with the study's primary endpoint focused on evaluating the cancer's clinical or pathologic response during post-therapy (i.e., at the time of surgery). For example, years of clinical research studies have strongly demonstrated that neoadjuvant chemotherapy given to the patient prior to surgery 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 begins with preclinical, or non-clinical, research in the laboratory. Non-clinical studies are those that do not involve human subjects, but instead involve animals. Preclinical or non- clinical studies are necessary to gather information including toxicology, pharmacology, and pharmacokinetics to support clinical research in humans.

Clinical trials can only be undertaken if the pre-clinical findings suggest that the new drug or treatment is likely to be safe *and* will work in humans. Pre-clinical studies, also called laboratory studies, include:

- **Cell studies**: These are often the first tests done on a new treatment. For instance, to see if it might work, researchers look for effects of the new treatment on cancer cells that are grown in a lab dish or a test tube. Since this is pre-clinical, these studies may be done utilizing human cancer cells or animal cancer cells.
- **Animal studies**: Treatments that look promising in cell studies are tested next in live animals. This gives researchers an idea of how safe the new treatment is in a living creature.

Although pre-clinical studies provide valuable data, they cannot offer all the necessary information to determine whether the study should move forward. This is because humans, compared to other vertebrates (such as mice and rats), can be very different in the way they absorb, metabolize (i.e., process), and get rid of drugs or treatments from their systems. For example, a treatment that works well at treating cancer cells within a mouse might or might not work in people. Moreover, there could also be side effects and other serious problems that would not appear in animal studies but could show up when the same drug or treatment is introduced in human subjects. Nonetheless,

if the pre-clinical studies are completed and the treatment still seems promising, the study team will need to reach out to the US Food and Drug Administration (FDA) to receive permission before testing the treatment in human subjects.

Clinical Studies

There are many ways to categorize clinical studies. Following is a description of the phases in investigational drug studies. Later in this chapter we will also review how Investigational device studies are categorized, which are done in a slightly different way than investigational drug or biologic studies.

H. 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, new route of administration, 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. In addition to pre-clinical studies already described above, 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 (e.g., for a brief time), with no therapeutic or diagnostic goals. Phase 0 studies use only a few small doses of a new drug in a few people (usually 15 people or less). The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies may help researchers find out if the drugs do what they are expected to do. This may help save time and money that would have been spent on later phase trials.

Unlike other phases of clinical trials, there's almost no chance the human participants in phase 0 studies will benefit from their participation in this phase of the study. Any benefits, if they do occur from the study drug or treatment, will most likely only happen to future participants in later phases of the study. Moreover, since the drug doses given to the participants are so low, there's also less risk to those that participate in this phase in the trial.

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. Placebos (inactive treatments) are not used in phase I trials. Phase I studies are usually brief, and the study researchers monitor the development of all adverse events closely, including their severity and frequency, since this information will provide the foundation for the future "side effects" that may be listed if this drug should get to market.

Though Phase I studies are primarily concerned with assessing a drug's safety, they are also done to determine the metabolism and pharmacologic actions (i.e., the uses, effects, and modes of action) of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness. Therefore, the overall purpose of this phase of the study is to determine **safety and dosage**.

Since 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 (e.g., 20 to 100 healthy volunteers). Phase I studies could also enroll a small number of diagnosed patients with the disease/condition of interest who have not been helped by previous treatments. As a result, sometimes people choose to join phase I trials when they have failed all other treatment options.

Phase I trials carry the most potential risk, especially to diagnosed patients who have not been helped by other treatments for their disease. However, there are some phase I studies who are able to offer some help to a select few patients. For those with life-threatening illnesses, weighing the potential risks and benefits carefully is key to determining whether to participate. This is because while some people may benefit from being on one, disease response is not the main purpose of a phase I trial.

Per the US Food and Drug Administration (FDA), as of January 4, 2018, approximately 70% of Phase I drug studies move to the next phase in research.

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 anywhere from several months to a couple of 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 (i.e., up to several hundred people with the disease/condition) to see if it is effective and to further evaluate its safety. Although these studies involve a few hundred patients, they are not considered large enough to statistically demonstrate whether the drug will be beneficial to treat the disease or condition. Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols. Therefore, the purpose of this phase of the study is to determine **efficacy and side effects.**

According to the US Food and Drug Administration (FDA), as of January 4, 2018, approximately 33% of Phase II drug studies move to the next phase of research.

Phase III: (Therapeutic Confirmatory)

Phase III studies gather more information about the drug or treatment's safety and effectiveness by studying its effects on different populations as well as by studying different dosages on those populations. 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. Phase III studies typically last longer than two years to gather long term safety data.

The study drug is given to large groups of people (i.e., 300 to 3,000 volunteers) in the target (i.e., individuals with who have the disease or condition) patient population. Researchers confirm effectiveness, monitor side effects, and compare to commonly used treatments. In previous studies and/or phases, it is possible that less common side effects might have gone undetected. However, because these studies involve a larger population and are typically longer in duration, the results are more likely to show long-term or rare side effects. Therefore, the purpose of this phase is to document **efficacy as well as monitor adverse reactions**.

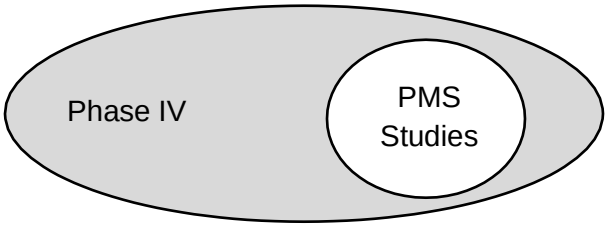
As of January 4, 2018, approximately 25-30% of drugs in this Phase III move to the next phase of

research per the US Food and Drug Administration (FDA).

Phase IV: (Therapeutic Use)

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. The population required for this phase is also quite large and can enroll several thousand volunteers who have the disease/condition. Phase IV studies also gather additional information used to determine cost effectiveness, drug compliance, or the drug's impact on quality of life. The purpose of this phase of the study is to establish the **safety and efficacy** of the proposed new treatment for a disease or condition.

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.

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/or only makes claims to **improve overall health** or offers a broader, more vague statement about its effects, it is regulated as a dietary supplement.

I. 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 to 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 (NSR)** device study is one that does not meet the definition of a significant risk device study. A convened IRB (i.e., a scheduled full board meeting) can make the determination that a device is NSR.

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 drug labeling, IRB approval, informed consent, monitoring, records, and reports. However, there is no need to make progress reports or final reports to the FDA under these abbreviated requirements.

An **exempt** device is a diagnostic device, in which the tests are noninvasive and do not 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 that 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.

510(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.

J. Study Design

The study design describes the strategy by which interventions or therapies are assigned to participants in a clinical study. There are several types of intervention models, including Single group design, Parallel design, Crossover design, and Factorial design.

This chapter will not go into significant detail into each design, but rather give a broad overview so all members of the study team have a general understanding of the study design. These descriptions should allow the research staff to interact with study participants more successfully by helping them to be able to describe the study design in layman's terms.

There are several types of intervention models, including Single group design, Parallel design,

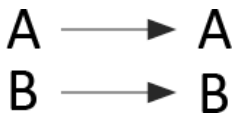
Crossover design, and Factorial design.

Single Group

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

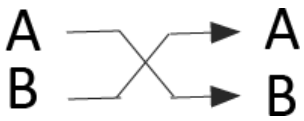
Parallel

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

In addition to intervention models, the study's design can also be described by other ways, such as who will receive treatment (controlled versus uncontrolled), how often the investigational treatment is required for the enrolled subjects (single or multiple dose), how many centers will be involved (single versus multi-center), and whether the staff will be aware of who receives treatment on the study (i.e., blinding). The following section explores these additional standards.

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.

Conversely, an uncontrolled study is when all participants are given a treatment and simply followed for a period of time to see if they improve, with no comparison against another group (control group) that is either taking another treatment or no treatment at all.

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

Some studies look at one or more (i.e., multiple) treatments, or doses, in comparison to each other. The main difference between a multiple dose study and a single dose study is the number of doses given to individual study subjects. However, single dose studies are almost always performed first to obtain a rough understanding of the drug's single dose pharmacokinetics (the study of drug absorption, distribution, metabolism, and excretion) before the study researchers move to a multiple dose. The various treatments and/or doses used should be outlined in a detailed protocol for the study researchers to follow.

Single Site or Multi-Center

Some clinical research studies are conducted at a single site (such as UT Southwestern), while

multi-center studies are conducted at more than one study site (e.g., at various hospitals across the United States as well as in Europe). There are pros and cons to choosing one type over the other. For instance, a multi-center study allows for a larger pool of research subjects, more genetic variety from the subjects (if that is an area of interest in the study), and the ability to compare results across centers, all of which contributes to the overall generalizability of the study. On the other hand, a multi-center study has higher costs associated with staffing/managing the study in addition to methodological, implementation and statistical challenges. The protocol will indicate whether the study is a single or multi- center study.

Blinded or Unblinded

Open Label or Unblinded

Blinding, also known as "masking," refers to the research activity of purposely withholding information regarding the assigned treatment from one or more participants in a clinical research study. It is an essential methodological feature of clinical studies that helps to maximize the validity (what an instrument measures and how accurately it does so) of the research results.

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. Or, the study may be designed so that some patients receive an additional infusion, while others receive the standard of care. Or one study drug creates a distinct color when it's reconstituted (i.e., adding a liquid diluent, such as sterile water or bacteriostatic water, to a dry powdered drug to make a liquid with a specific concentration) by the investigational pharmacist, while the standard treatment appears clear when it is delivered bedside. In all of these situations, it would be impossible to not know which treatment arm the patient has been randomized to because the differences are so apparent.

Blinded: Single-blind (single masked)

In a single-blind trial, ***either*** the investigator ***or*** the subject are aware of the details of the study treatment. In practice, if one of them knows the treatment that is being received, it is possible for that person to subconsciously relay important treatment-related details to the other person, thus introducing bias (i.e., any tendency that limits impartial consideration of a question or issue; a type of systematic error that can distort measurements and/or affect investigations and their results) and influencing the study outcome.

Blinded: Double-blind (double masked)

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, to the subjects.

Randomized, double-blind placebo-controlled trials involve the random placement of participants into two (or more, if there are multiple investigational dose) groups; an experimental group that receives the investigational treatment and a control group that receives a placebo (a harmless substance made to resemble the investigational treatment). Neither the researchers nor the research subjects know who is receiving the experimental treatment and who is getting a placebo. This type of clinical study is widely considered the gold standard for the validation of treatment interventions. Therefore double-blind, or "randomized," studies are preferred as a design, as they limit the potential for bias.

It's important to note: the blind, whichever one is utilized in the study, should be maintained at all times by the study staff. In cases of emergency (e.g., a subject is experiencing a severe allergic reaction during treatment and the investigator needs to know which one it is), there are procedures to be followed so that the blind can 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

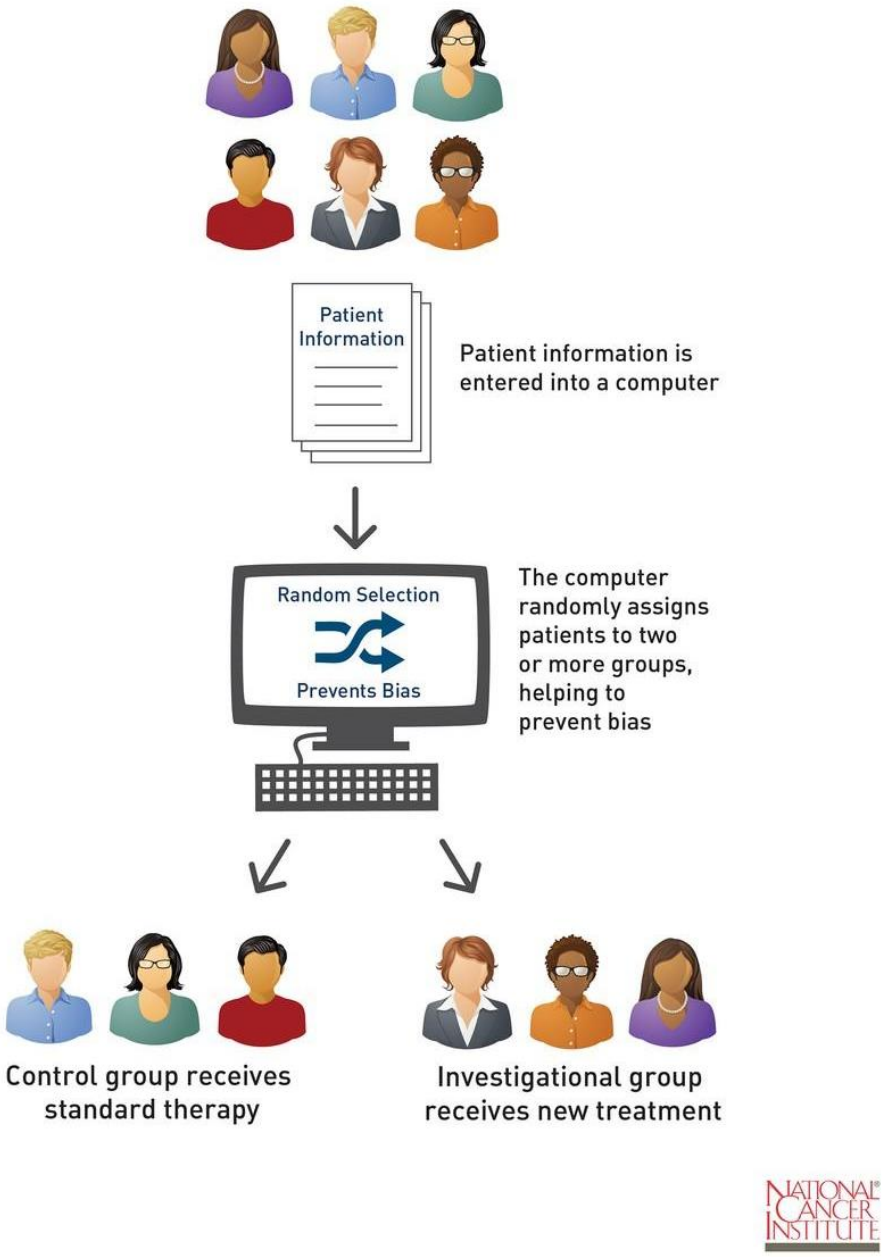
Randomization is a method used to prevent bias in research. The randomized study is generally considered the most reliable form of scientific evidence because it is the most widely accepted design for eliminating the variety of biases that could compromise the validity of the research. This is because when it is applied correctly to a study design, randomization eliminates bias by distributing the characteristics of patients that may influence outcome randomly between treatment groups so that any difference in outcome can be explained only by treatment. In a randomized

study this is achieved by any number of methods, such as a computer or table of random numbers, which then determines the treatment assignments. Thus, participants have an equal probability to be assigned to one of the various groups.

At several points during (e.g., through interim analysis, where all accumulated data is analyzed and findings are used to make any necessary adjustments to the ongoing study) and at the end of the clinical trial, researchers will compare the data from the randomized groups to determine which treatment is more effective or has fewer side effects. Consequently, the fundamental benefits of randomization include the following:

1. Eliminates selection bias introduced by the researchers. Selection bias occurs when the selection of subjects into a study (or their likelihood of remaining in the study) leads to a result that is methodically different to the target population.
2. Balances all treatment arms with respect to potential variables (both known as well as unknown by the person and/or staff that developed the protocol)
3. Forms the basis for stronger statistical tests based on an assumption of the equality of treatment assignments

In sum, a randomized trial is an essential tool for testing the efficacy of the treatment in clinical research and ensures the scientific validity of the results.



Source: clinical-trial-randomization-infographic.jpg (992×1299) (cancer.gov).

There are several potential types of randomizations in research and the study protocol will identify the type of randomization utilized in the study design, 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. In this handbook, we will briefly discuss the three most popular types of randomizations in clinical research: Simple, Block, and Stratified.

Simple randomization

In simple randomization the subjects are randomly allocated to experiment/intervention groups

based on a constant probability. In other words, if we divide all enrolled subjects into two groups called A and B, each subject has a 0.5 (50%) probability of being assigned to either group A or group B. The activity of allocating subjects to either group can be performed in multiple ways, such as flipping a coin, assignments drawn from random tables or numbers, just to name a few.

The benefit of using this methodology is that it eliminates selection bias since probability drives the assignment allocation. However, a disadvantage of utilizing this methodology is a potential imbalance in the number allocated to each group (if the study has a planned small sample) as well as the prognostic factors between groups.

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. The aim of block randomization is to balance the number of subjects allocated to each experiment/intervention group.

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

The disadvantage with block randomization is that there is still an aspect of expectedness in how subjects are selected and the randomization of prognostic factors (e.g., predictions of how a disease is likely to affect a patient on the study) is not taken into consideration. Nonetheless, block randomization guarantees that at no time the imbalance will be too great and at certain points the numbers of participants in each group should be mostly equal.

Stratified

In stratified randomization, the study subjects are defined based on specific pre-determined strata, which are commonly referred to as covariates. An example of a covariate is a variable that is observed (rather than manipulated) and may impact a study's outcome. Stratified randomization allows the researchers to further refine the groups in which subjects will be placed based on these covariates. The sample size necessary to reach a clinically significant result will help determine the number of strata required for the study design.

In the example below, enrolled subjects are divided up into two groups based on gender assignment at birth, such as female and male sexes, and then randomized to their treatment.

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

Any covariates utilized in the study design needs to be carefully assessed and clearly identified before the randomization process can be initiated. Any missteps in identifying the appropriate covariates will have a significant impact on the final validity of the results. The benefit of stratified randomization is that it enables comparison between experiment/intervention groups, thus making the process of analyzing conclusions more efficient.

Chapter 2: UTSW Clinical Research Infrastructure, Policies, Agencies and Affiliated Hospitals

This chapter provides a brief overview of the entities involved in the oversight of clinical research at UT Southwestern. Clinical research at UTSW is supported by many diverse entities that vary greatly in size, scope, and level of involvement. 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 encounter all of the offices or committees described in this chapter, but all those involved in clinical research should be aware of the services that each offers to support research activities at UT Southwestern.

A. Human Research Protection Program

The Human Research Protection Program (HRPP) provides oversight of all research activities involving human subjects at the UTSW. The HRPP is a collective effort of all who participate in the conduct, review, approval and facilitation of Human Subjects Research at UTSW. The HRPP's goal is 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.

The HRPP responsibilities are carried out by the following offices:

IRB (IRB) Office – Responsibilities include:

- UTSW IRB review – Research reviewed by one of four UT Southwestern IRBs or by a UTSW IRB Expedited Reviewer
- Non-UTSW IRB Review (sIRB/Reliance) – Collaborative research reviewed by a single IRB (either UTSW IRB or a non-UT Southwestern IRB)

Quality Assurance and Monitoring (QAM) Responsibilities include:

- Routine and for cause monitoring
- Support to investigators before, during, and after regulatory audits

Regulatory Support Office (RSO) – Responsibilities include support for investigators with:

- Clinicaltrials.gov registration and reporting requirements
- FDA sponsor investigator submission and reporting requirements for an IND or IDE
- FDA submissions for Expanded access/ single patient use

The HRPP policies address the review, approval and conduct of human subjects research at

UTSW. 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. UT Southwestern HRPP Policies are available on the HRPP homepage in an index and are searchable by full-text and keyword: https://www.utsouthwestern.edu/research/hrpp/policies/.

B. UT Southwestern Institutional Review Boards

Researchers send their human research subjects protocols to the IRB or HRPP and depending on the level of review required or whether review is conducted through an external IRB, the protocol may be reviewed under expedited review (i.e., with a Senior Regulatory Analyst) or assigned to the next available institutional review board (IRB) meeting. Studies reviewed using an external IRB will undergo administrative review. IRB-specific policies and procedures can be found here.

The Institutional Review Board is charged with the responsibility of reviewing, prior to its initiation, research involving human participants. The IRB is primarily concerned with ensuring that the rights, welfare, and privacy of human participants are protected. The UTSW IRB has received full accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP), which indicates that UTSW follows rigorous standards for ethics, quality, and protections for human research.

The IRB has the authority to approve, require modifications in order to approve, disapprove, suspend, terminate, and observe the consent process for research that falls within its jurisdiction as specified by both the federal regulations and institutional policy. Each IRB must have at least five members of varying backgrounds to provide a complete and adequate review of human research and its safety, institutional, legal, scientific, and social implications. Each Board will also include at least one member who is not affiliated with the institution and one member who is not a scientist. The UT Southwestern IRBs have several consultants who advise the Board and are periodically involved in protocol review as necessary.

Additional facts about UT Southwestern's IRB:

- Four regularly occurring IRBs that meet twice per month (~8 IRB meetings a month)
- Each IRB reviews all types of research (biomedical and social/behavioral)
- Each IRB has ~18 members where each member serves a 3-year term
- UTSW has approximately 5000 active protocols at any given time
- UTSW is the IRB of record for partner institutions

The UT Southwestern Medical Center IRBs may provide review and continuing oversight of some, or all research conducted at affiliated institutions. Institutions relying on the UTSW IRBs remain responsible for ensuring compliance with the IRB's determinations and the terms of its OHRP approved FWA, as applicable.

Finally, UT Southwestern IRBs may also agree to defer to another institution's IRB, or a central IRB. For instance, UTSW routinely defers to the **Advarra IRB and WCG IRB** and the **National Cancer Institute's Central IRB (CIRB).** These efforts are managed through the Single Institutional Review Board (sIRB). The purpose of using sIRB is to encourage collaboration, reduce duplicate study submissions, and minimize the impact of multiple IRB reviews for the same protocol. For more information about the role and responsibilities of the sIRB at UT Southwestern, please go to https://www.utsouthwestern.edu/research/hrpp/sirb/. For IRB-specific policies and procedures, please visit: https://www.utsouthwestern.edu/research/hrpp/irb/.

Within the IRBO, the **Regulatory Support Office (RSO)** provides additional services to support each of the following specific areas within clinical trial management:

- **ClinicalTrials.gov Reporting Support Program**: ClinicalTrials.gov is a *federally mandated* clinical trial registry and results database run by NIH that discloses key information of clinical trials to the general public. Failure to comply may result in public notices of noncompliance and violations, FDA sanctions, civil monetary penalties ($13,237 per day), withholding of grant funds, refusal to CMS claims and journal publication. RSO staff can assist the **Responsible Party** (i.e., UTSW Investigator) with ClinicalTrials.gov Reporting, which includes (1) Registration, (2) Updates, (3) Protocol Registration and Results System (PRS) comments in ClinicalTrials.gov, and (4) Results. More information is available here: ClinicalTrials.gov Support: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

- **FDA Submission Support Program**: UT Southwestern requires oversight of sponsor investigators. To provide necessary support and oversight, the HRPP requires that all IND/IDE submissions to the FDA also be reported to the HRPP Regulatory Support Office's SI Support Team. The RSO can assist the **Sponsor Investigator** with FDA submissions for IND, IDE, and Expanded Access. This includes (1) Preparation, (2) Submission, and (3) Maintenance. More information is available here: Sponsor Investigator (SI) Support: Human Research Protection Program (HRPP) – UT

Southwestern, Dallas, TX.

In addition to the above, the RSO also provides the following resources and educational materials:

- RSO Website: application templates, quick guidance documents, decision trees, and an educational video library
- Regulatory Education: best practice trainings, consultations via Booking

For more information about the RSO or to request a booking, please go to: Regulatory Support: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

C. UTSW Clinical and Translational Science Award Program

The NIH-funded UTSW Clinical and Translational Science Award (CTSA) Program is composed of five academic partners at UTSW including the Schools of Medicine and Public Health, Nursing, Pharmacy, and Veterinary Medicine, and the College of Engineering. UT Southwestern's CTSA is one among a national consortium of approximately 60 such awards whose purpose is to provide support to institutions, which is used develop programs designed to accelerate the translation of scientific discovery that will ultimately improve the health of our nation. The CTSA Program's goal at UT Southwestern is to advance the science of research translation, engage patients and the public in DFW, and provide tools, methods, and best practices to improve the health of the communities we serve.

To achieve its goals, the UT Southwestern CTSA Program has developed innovative strategies and solutions to improve the efficiency, quality, and impact of research conducted at UT Southwestern and our affiliates. This will result in turning observations from the laboratory, clinic, and community into interventions that improve the health of individuals and the public. CTSA Program's strategic goals for the future include:

- Advance translational science by capitalizing on our strengths in the biomedical sciences and accelerate translation of new therapies.
- Strengthen community stakeholder engagement.
- Promote flow of knowledge, tools, methods, and processes with the goal of improving quality, efficiency, safety, and value of clinical research.

To accelerate the translation of scientific discoveries to improved health, the CTSA Program at UT Southwestern offers resources to help you develop and carry out a successful research project. These include pilot grant funding, support services and research education programs including an array of ongoing seminars, webinars and community engagement grand rounds open to the entire

research community. CTSA assists researchers working with the FDA or clinicaltrials.gov. They offer sponsored 1:1 consultation for biostatistical support, assistance with determining study feasibility, recruitment through MyChart messaging, multisite studies, data sourcing and community engagement.

As a member of the clinical and translational research community at UT Southwestern, you are inheriting a wealth of information and established relationships to help you succeed in your role. Within this handbook, you will be introduced to all of the major programs within UT Southwestern's CTSA Program, who will explain their services and provide guidance so that you can successfully conduct clinical research studies from start to finish. Whether you are working as a research coordinator on an investigator-initiated study, supporting a PI developing a new study, or working on a multisite clinical trial, the CTSA Program can provide you with resources and strategies to optimize your role.

To review more about the CTSA's key research services and infrastructure supported for conducting clinical and translational research, please go to the following: https://www.utsouthwestern.edu/research/ctsa/.

D. Scientific/Ethical Committee

Simmons Comprehensive Cancer Center (SCCC) Protocol Review and Monitoring Committee (PRMC)

As a National Cancer Institute – Designated Comprehensive Cancer Center, The Protocol Review and Monitoring System (PRMS) within the Simmons Comprehensive Cancer Center (SCCC) provides independent peer review for scientific merit, prioritization, and monitoring for all cancer-related clinical and population science studies conducted at the UT Southwestern and its affiliated health care systems, Parkland Health and Hospital System and Children's Medical Center. PRMS approval is required before any cancer-related study can open at UT Southwestern Medical Center.

The PRMS has a two-stage approval process. The first stage of the protocol review is performed at the level of the disease-oriented teams (DOTs) to determine trial feasibility and portfolio diversity. Studies that pass the initial review at the DOT level qualify for submission to the Protocol Review and Monitoring Committee (PRMC) for second stage review.

Cancer-related outcomes or other study endpoints may reflect clinical treatment or quality of life,

change in attitudes/beliefs or behaviors, or healthcare delivery for either solid tumors or hematology/hematologic malignancies. Such studies can occur at any point along the cancer care continuum, including screening and early detection, diagnosis and treatment including palliation and symptom management, through survivorship, as well as end of life and hospice. These studies then may include enrollment or measurements of any of the following: 1) cancer patients, their caregivers or relatives 2) or cancer clinical care team members, 3) or individuals targeted for cancer prevention activities including lifestyle change, 4) or the assessment of cancer epidemiologic, imaging, or biological markers. If the study involves any of these factors the study must be reviewed by the PRMC.

The Protocol Review and Monitoring Committee consists of: PRMC #1, PRMC #2, and Population Science PRMC. PRMC #1 and #2 reviews protocols which are clinical interventional focused while Population Science PRMC reviews studies geared towards the science that are population-based research areas. The PRMC policies, guidance and training information are located on the PRMS SharePoint site: https://365utsouthwestern.sharepoint.com/sites/SCCC/SitePages/Protocol-Review-and-Monitoring-System.aspx

E. Safety Committees

Institutional Biosafety Committee (IBC)

The Institutional Biosafety Committee (IBC) is managed through the UT Southwestern Office of Safety and Business Continuity (Safety). IBCs have been established under the National Institute of Health (NIH) Guidelines. The IBC reviews research activities involving recombinant or synthetic nucleic acid molecules, infectious agents, human materials, and other potentially hazardous biological agents. Safety, primarily the Biological Safety Program, is the monitoring and effector arm of the Institutional Biosafety Committee (IBC) and UT Southwestern Administration. Safety provides administrative services for all IBC business operations.

UT Southwestern's IBC does the following on behalf of the institution:

- Ensure all research conforms with the NIH Guidelines, when applicable.
- Ensure all impacted healthcare providers are provided education on the hazardous biological materials (e.g., investigational drugs), their associated exposure risks and the proper methods to mitigate these risks.
- Ensure all necessary safety control measures, practices, and precautions are in place to support the safe handling of hazardous biological materials.
- Ensure healthcare providers have available all required personal protective equipment.

- Ensure investigators follow all institutional compliance processes (e.g., acquisition of IBC approvals).

Contact Safety when research involves:

- The deliberate transfer of genetic material into human research participants.
- Investigational drugs composed of live, attenuated, or genetically modified microorganisms.
- Collection of patient specimens and/or samples for onsite processing or storage (see flow chart for details: https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/biological/tip_sheet_human_subject_study.pdf).
- NOTE: Some research studies may be exempt from Human Subject Research by IRB specifications. Exempt from IRB registration does not indicate that these projects are exempt from IBC registration.

Information regarding IBC policies, guidance and training information are located on the IBC website: https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/biological/human-subject-studies.html

Subcommittee for Human Use of Radiation in Research (SHUR)

The Subcommittee for Human Use of Radiation in Research (SHUR) is managed by the Office of Safety and Business Continuity (OSBC) and is also a part of the Radiation Safety Advisory Committee (RSAC) at UT Southwestern. SHUR has been appointed to review all research protocols that require participants to be exposed to ionizing radiation for research purposes. SHUR is an ancillary committee that works with the Institutional Review Board (IRB). Studies submitted through the electronic Institutional Review Board (eIRB) that have been earmarked that radiation is involved are directed to SHUR for review and approval. SHUR ensures that patients participating in clinical studies will be informed of the research radiation procedures as well as provided accurate information about the risks associated with the research radiation procedures.

In addition to UT Southwestern Medical Center, SHUR also provides independent peer review for all clinical studies that use ionizing radiation at its affiliated healthcare systems:

- Parkland Health
- Children's Health
- Scottish Rite for Children
- Texas Health Resources

Ionizing radiation is a beneficial tool for both diagnostic and therapeutic clinical applications. However, there is a risk to the patients associated with radiation exposure. For clinical uses of radiation, it is generally believed the benefit of the exposure to ionizing radiation outweighs the risks. All research studies with radiation procedures are reviewed. Research studies with only medically indicated radiation procedures are reviewed by the IRB. Each IRB has a SHUR faculty member that will review the radiation safety aspects of the research study when the study goes for IRB review. Research studies that include radiation procedures for research use are reviewed by SHUR and IRB. SHUR radiation safety approval is required for all modalities of ionizing radiation for research. This includes diagnostic imaging (CT, x-ray, fluoroscopy), interventional radiology, radiopharmaceuticals (both diagnostic and therapeutic uses), and radiation therapy. It is important to note that some clinical procedures outside of Radiology may use ionizing radiation (e.g., surgical procedures, cardiac catheterization procedures). It is also important to note that magnetic resonance imaging (MRI) does NOT use ionizing radiation; thus, research studies with only MRI procedures do not need to be reviewed by SHUR.

The members who comprise SHUR include faculty from various clinical departments that use ionizing radiation – this includes the Department of Radiology (including the Medical Physics Division, Nuclear Medicine Division, and Breast Imaging Division), Department of Radiation Oncology, and Department of Pediatrics – and OSBC Radiation Safety leadership. SHUR faculty members perform the radiation safety reviews for research studies that result in a radiation dose greater than 5,000 mrem from research procedures. Radiation Safety leadership performs the radiation safety reviews for research studies that result in a radiation dose less than 5,000 mrem from research procedures. The OSBC Radiation Safety Program serves as the committee liaison and corresponds with the principal investigators and research coordinators. SHUR will issue radiation safety approvals through the eIRB. For research studies where changes are needed, SHUR will issue letters with stipulations through the eIRB.

The SHUR radiation safety review encompasses a review of the following for each research study: the eIRB smart form, the study protocol (and investigator's brochures, if applicable), and the study consent form(s).

For the eIRB smart form, it is important that the radiation procedures (both those that are medically indicated and those that are for research use) are properly documented. When entering the radiation procedures in the eIRB smart form, you should consider the following:

- Are all procedure types for each radiation modality listed correctly?
- Does each procedure have the correct effective dose listed?

  - Study team can reference the SHUR exam tables. The exam tables include dosimetry information for the most commonly used radiation procedures
  - Study team can reach out to SHUR for assistance. If the research study is using a new radiopharmaceutical, then Medical Physics will need to be consulted to evaluate the dosimetry information. Medical Physics can also assist with providing estimates of the effective dose for radiation procedures that are not listed on the exam tables
- Does each procedure list the correct number of exams?
- Does each procedure correctly indicate which exams are used for research or medically indicated?
  - This determination affects the risk statement used in the study consent form. The patient will be reading the consent form to understand risks associated with the research study – it is important that we provide the appropriate radiation risk statement. Thus, it is important that the number of procedures for research use are correctly indicated
  - This determination also affects who will be performing the radiation safety review – SHUR faculty or Radiation Safety leadership
- Is the research study using a radioactive new drug or biological product that is not approved by the FDA?
  - The study team should include an Authorized User (AU) listed on the institution's radioactive materials license. This can be confirmed by the Radiation Safety program. The Aus are typically faculty within the Nuclear Medicine Division of the Department of Radiology
  - The smart form should list the IND number for the radiopharmaceutical and include a copy of the IND letter from either the FDA or study sponsor to show the IND is approved
  - The smart form should include the Investigator's Brochure – this has important information for evaluating radiation doses

For the study protocol, it is important that all radiation procedures included in the research study are identified and documented in the eIRB smart form. Relevant information is typically included in the Schedule of Events or Schedule of Activities. When reviewing the study protocol, you should consider the following:

- Are all radiation procedures included in the study protocol documented in the eIRB smart form?
  - It is important to review the footnotes for the Schedule of Events or Schedule of

Activities. Sometimes alternate exams will be listed in the footnotes without being a line item in the schedule/table

- It is important to review the inclusion/exclusion criteria. There may be radiation procedures required at screening to satisfy the inclusion and/or exclusion criteria. There may be radiation procedures listed as alternatives to study procedures (e.g., CT study for patients that have contraindications for MR imaging)
- It is important to read the written portion of the study protocol about the radiation procedures. There may be more detail in this section that describes the type and frequency of the radiation procedures. Any alternative radiation procedures may be listed in this section, too (e.g., multi-gated acquisition (MUGA) scan as an alternative for echocardiogram (ECHO) procedure)

- Common radiation procedures that are missed in the eIRB smart form:
  - CT studies for patients that have contraindications for MR imaging
  - Procedure needs to take into account all areas to be imaged (CT Chest, CT Abdomen/Pelvis)
  - Monitoring for adverse events may call for imaging procedures (CT study)
  - Some procedures that use ionizing radiation do not include “radiation” in the procedure name (i.e., MUGA, bone scan, port/catheter/needle placement, transjugular liver biopsy, lumbar puncture, transarterial chemoembolization (TACE))

For the study consent form(s), it is important that all radiation procedures included in the research study are identified and documented along with any appropriate risk statements. This is the document that the patient will be reading to better understand the procedures that are included in the research study and the associated risks. When drafting the study consent form(s), you should consider the following:

- Are the radiation procedures used for research clearly identified?
- Are the radiation procedures medically indicated clearly identified?
- For research studies using the UT Southwestern IRB:
  - Please use the SHUR-approved risk statements. This includes the radiation risk statement and pregnancy risk statement (if applicable for radiopharmaceuticals).
  - Please do not use any other risk language for the radiation procedures for research uses.
- For research studies using a CIRB or other outside IRB, please ensure the radiation risk statement accurate for the radiation procedures for research uses.
- Medically indicated radiation procedures do not require a radiation risk statement.

Please refer to the SHUR website for additional information and guidance, including guidelines for what constitutes radiation for research, radiation procedure exam tables (for dosimetry information), and various SHUR-approved risk statements: https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/radiation/rad-subcommittees/subcommittee-for-human-use-of-radiation.html.

Radioactive Drug Research Committee (RDRC)

The Radioactive Drug Research Committee (RDRC), similar to the IBC, is managed through the UT Southwestern Office of Safety and Business Continuity (OSBC). RDRC is chartered by the FDA under the provisions of 21 CFR 361.1, *Radioactive drugs for certain research uses*. The RDRC reviews and approves certain basic research using radioactive drugs in humans *without* an Investigational New Drug (IND) application. The following information in this section is taken directly from the FDA *Guidance for Industry and Researchers – The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application* published in August 2010 (https://www.fda.gov/media/76286/download).

The FDA has two pathways that allow for the investigational use of radioactive new drugs and biological products: the most common pathway is the investigational new drug (IND) application (21 CFR 312), and the second pathway is the RDRC approval (21 CFR 361.1). The RDRC is intended to review and approve the investigational use of radioactive drugs for certain research purposes, specifically basic science research. For research purposes outside of the scope of the RDRC, these research studies involving the investigational use of radioactive new drugs must be conducted under 21 CFR 312, *Investigational New Drug Application*. The RDRC does not review research that is intended for immediate therapeutic, diagnostic, or similar purposes, or to determine the safety and effectiveness of the radioactive drug or biological product for such purposes (i.e., the research cannot constitute a clinical trial for the product).

Examples of the types of basic science research that would be appropriate to conduct under an RDRC without an IND include the following:

- Metabolism and excretion studies (including kinetics, distribution, dosimetry, and localization) of a radioactive drug
- Noninvasive functional imaging/molecular imaging studies for human physiology, pathophysiology, or biochemistry
    - Biodistribution
    - Pathophysiology

- Receptor binding or occupancy
- Transport processes
- Enzyme activity
- Multistep biochemical processes

The FDA regulations (21 CFR 361.1) list three additional requirements for human subject research that may be conducted under an RDRC:

1. The research must be approved by an RDRC that is approved by FDA (21 CFR 361.1(b)(1) and 21 CFR 361.1(c)(4)) – UT Southwestern RDRC is approved by the FDA.
2. The dose to be administered must be known not to cause any clinically detectable pharmacological effect in humans (21 CFR 361.1(b)(2)). This requirement means that RDRC protocols cannot include the use of drugs that have no documented previous human experience.
3. The total amount of radiation to be administered as part of the study must be the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and must be within the specified limits (21 CFR 361.1(b)(3)).
    a. Limits on Radiation Dose for Adults:
        i. From a single study: 3 rem for whole body, active blood-forming organs, lens of the eye, gonads; 5 rem for other organs.
        ii. Annual and Total dose: 5 rem for whole body, active blood-forming organs, lens of the eye, gonads; 15 rem for other organs.
    b. The radiation dose to an individual subject consists of the sum total of all sources of radiation associated with the research protocol including the following:
        i. The radiation absorbed dose from the radioactive drug (including any significant contaminant or impurity)
        ii. The radiation absorbed dose from any associated x-ray procedures, and
        iii. The radiation from any follow-up studies.

Investigators will need to provide the following information as part of the RDRC application:

- Qualified study investigators (21 CFR 361.1(d)(3))
- Proper licensure to handle radioactive materials (21 CFR 361.1(d)(4))
- Appropriate selection and consent of research subjects (21 CFR 361.1(d)(5))
    - FDA recommends that an RDRC protocol be approved for a finite number of subjects sufficient to gain basic information. Many studies under an RDRC start with 30 research subjects or fewer.
    - If the number of research subjects is greater than 30, the RDRC must submit a

special summary of information immediately to the FDA and receive FDA approval prior to approval by the RDRC.

- Appropriate quality of radioactive drug administered (21 CFR 361.1(d)(6))
- Sound research protocol design (21 CFR 361.1(d)(7))
- Reporting of adverse events to the RDRC (21 CFR 361.1(d)(8))

In addition to the initial protocol review and approval, the RDRC must review and approve all protocol amendments. All adverse events (AE) associated with the use of the radioactive drug must also be reported immediately, but no later than 7 calendar days, to the RDRC. The RDRC must report immediately, but no later than 7 calendar days, to FDA all AEs probably attributable to the use of the radioactive drug. When RDRC review is required, approval must be obtained before the IRB will review and approve the protocol.

Please refer to the RDRC website for additional information and guidance: https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/radiation/rad-subcommittees/radioactive-drug-research-committee.html.

Stem Cell Research Oversight (SCRO) Committee

The Stem Cell Research Oversight (SCRO) Committee provides oversight for all research on campus involving: the use of human embryos, human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs).

The state of Texas does not require oversight of this work. However, UT Southwestern reviews this scope of work (ESC/iPSC) out of good ethical practice.

Following are pertinent guidelines observed by the SCRO committee:

- National Academy of Sciences Guidelines for Human Embryonic Stem Cell Research: Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research |The National Academies Press
- International Society for Stem Cell Research (ISSCR) Guidelines for Stem Cell Research and Clinical Translation (amended 2021): Guidelines — International Society for Stem Cell Research (isscr.org)
- National Institutes of Health Guidelines for Human Stem Cell Research (if PHS funded): NIH Guidelines for Human Stem Cell Research | STEM Cell Information

Texas law has impacted the ability to acquire certain materials for stem cell research at UTSW. On June 6, 2017, Governor Greg Abbott signed into law the Texas Health and Safety Code chp. 173 (formerly Senate Bill 8) with an effective date of September 1, 2017. One provision in this bill prohibits the sale and purchase of human fetal tissue as well as some methods of human embryo procurement, which can impact certain type of biomedical research.

If you intend to publish your stem cell research, the SCRO committee has recommendations for Manuscripts. All SCRO policies, guidance and training information are located on the SCRO website (https://www.utsouthwestern.net/intranet/research/scro/).

Laser Safety Committee

The Laser Safety program actively supports all staff, faculty, and residents with the use of lasers across campus. This includes UT Southwestern Medical Center, Aston Clinics, Children's Medical Center, Parkland Memorial Hospital, William P. Clements Jr. University Hospital, Clements University Hospital – Zale Lipshy Campus, and Veterans Affairs Medical Center, as well as all of the outpatient clinics.

The Laser Safety staff evaluates recommendations for the purchase, maintenance, repair, documentation, registration, utilization, disposal, and administration of all medical lasers. Laser safety is responsible for monitoring operations of all lasers to ensure compliance with national, state, and institutional regulations and policies. The laser safety team also organizes and supports the Campus Laser Safety committee meetings and plays a significant role in ensuring that national and state regulatory issues are addressed.

The laser safety team also plays a significant role in the training and education of the staff, faculty, and residents on the basic physics of lasers and light-tissue interactions and safety. Being a part of the largest medical laser program in the nation means that the laser safety program is responsible for researching and at times, developing breakthrough new procedures.

- Laser safety helps develop 1-2 new procedures annually
- The total number of procedures has increased an average of 15% a year over the past 10 years
- There are 245 lasers in labs, clinics, and surgical rooms at UT Southwestern and its affiliated hospitals
- On average Laser Safety performs 8,900 light-based surgical and therapeutic procedures

With their academic and developmental involvement in medical laser procedures, the staff has a

unique ability to gauge and review most of the new and emerging light and noninvasive technologies being brought to bear in today's changing surgical and clinical world. In the past few years, the staff has had the honor and pleasure to be involved with revolutionary new laser and light applications that significantly affected both the quality and duration of patient's lives. The laser committee's policies, guidance and training information are located on the laser committee's website (https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/laser/).

F. Other Approvals and Resource Offices

Advanced Imaging Research Center (AIRC)

Located in the Bill & Rita Clements Imaging Building on the UTSW North Campus, the Advanced Imaging Research Center Human MRI Core (HMRIC) facility offers dedicated research MRI services to more than 120 Principal Investigators in the Dallas area, including, but not limited to, UT Southwestern, UT Dallas, UT Arlington, Texas Health Resources, and Children's Medical Center Dallas.

The primary mission of the Advanced Imaging Research Center is to advance MR technology for the basic understanding and treatment of a wide range of human diseases such as cancer, diabetes, obesity, Alzheimer's Disease, psychiatric disorders, inborn genetic disorders, and diseases of the heart, lung, and liver. Utilizing high quality research data, higher field strengths, advanced imaging techniques, faster gradients, improved coil technology, and more robust sequence protocols, world-renowned experts assist researchers to advance diagnostic and treatment protocols from research to the clinical setting.

The AIRC allows access to all imaging instrumentation, providing data acquisition and analysis services. Major equipment that is offered at the AIRC includes: 3T Siemens Prisma MR system ("3TA"), 3T Philips Achieva MR system ("3TB"), 3T GE Discovery 750w MR system ("3TC"), 7T Philips Achieva MR system, and a GE 5T SPINlab Clinical Polarizer. The HMRIC facility provides technical (i.e., data acquisition/analysis, protocol development) and nursing support to whole-body 3T and 7T MRI scanners. Training undergraduate and graduate students to lead imaging research in the future is also a high priority.

If you plan to do a research study that involves one of the machines located at AIRC, your study will require review by the **HMRIC Protocol Review Committee**. Download the AIRC Application for Research with Humans for New 3T or 7T Service Projects and submit your application to the PRC Administrator for review.

For more information about policies related to the various imaging modalities and to submit an application, refer to the AIRC website (https://www.utsouthwestern.edu/education/medical-school/departments/airc/.

Conflict of Interest (COI) and Institutional COI (ICOI) Committees

UT Southwestern Medical Center, the Conflict of Interest (COI) Committee, and the Conflict of Interest (COI) Office ensure that relationships with outside entities do not:

- Bias the design, conduct, or reporting of research
- Detract from teaching, research, clinical, or administrative responsibilities
- Influence the research training of students or trainees
- Result in improper transfers of state resources

The COI policies, guidance, and information, addressing personal financial interests and outside activities, are located on the COI Program's dedicated website (https://www.utsouthwestern.edu/research/research-support/conflict-of-interest/) and in the Office of Research Support and Regulatory Management description in this Handbook. Additional resources are located in the following chapter within the HRPP Policy and Procedure Manual: 5.3 Financial Conflict of Interest Management.

The COI Program also addresses Institutional Conflict of Interest (ICOI), which may exist when the interests of the institution or those of an institutional leader have the potential to impact or bias certain activities, like research decisions, at UTSW. The ICOI Committee and COI Office identify ICOIs that may arise from UTSW's ownership interests, licensing, gifts, or certain interests or responsibilities of high-level leaders, and determine how to appropriately eliminate or manage them. The ICOI Committee is comprised of senior faculty members and administrators, as well as at least one non-affiliated member.

After ICOI evaluation, a Management Plan is issued which details the strategies required for managing or eliminating the conflict. ICOI Management Plans may include a variety of requirements, including disclosing UTSW's interest in informed consent documents for study participants as applicable. When specific informed consent language is required, the Management Plan will include this directive and be provided to all relevant individuals and the OHRPP. The COI Office supports the ICOI Committee and monitors adherence to ICOI Management Plans.

ICOI review is not based on any regulatory requirements. However, both AAHRPP and UT System

require that human research programs and institutions maintain ICOI programs.

UT Southwestern's policy on institutional conflict of interest (ICOI) is located here: https://secure.compliance360.com/ext/Ehc2hXLwZ_o=. Reach out to the COI Office with any questions on this topic: Conflict of Interest (COI) – Research Administration (utsouthwestern.net)

Information Systems Acquisition Committee (ISAC)

Information Systems Acquisition Committee (ISAC) governs the acquisition of information systems, related equipment, and software for the UT Southwestern Medical Center campus. The Committee has these goals:

- Reduce institutional technology risk
- Decrease redundancy and technology sprawl
- Drive cost savings

The Committee has established a process to streamline and clarify what requesters need to complete and provide for an acquisition request. The ISAC policies, guidance and training information are located on the ISAC website: (https://www.utsouthwestern.edu/employees/information-security/isac/).

Communications, Marketing, and Public Affairs (CMPA)

There is no other organization exactly like UT Southwestern Medical Center. The Office of Communication, Marketing, and Public Affairs (CMPA) oversees the use of UT Southwestern Medical Center branded materials.

When someone sees the UT Southwestern Medical Center logo, there should be no doubt that it stands for us alone. A logo is the foundation of an institution's brand. Strong brands always leave a clear, unmistakable impression, and we are responsible for that impression. When we are consistent in how we use our logo, colors, and all other elements associated with our brand, we strengthen the trust people place in us. We strengthen people's perception of our excellence.

Elements of the updated UT Southwestern Medical Center brand have appeared in marketing materials for several years, including the UT Southwestern tagline: "the future of medicine, today." This line, when combined with the UT Southwestern logo, reinforces the meaning of our brand.

If you are creating research materials that will utilize the UTSW brand and/or logo and be viewed by the public offsite, then the asset will likely need to be reviewed by the CMPA to ensure

compliance with their standards. If the materials will be utilized for research purposes, such as recruitment (e.g., flyers and ads encouraging hospital patients to participate in a study, whether in paper format or electronically shared on a social media website, for example), then the assets will also likely require review and approval by the UT Southwestern IRB prior to dissemination.

For guidance regarding CMPA's internal approval process, reach out to them via email at: CMPAClinicalTrials@utsouthwestern.edu. For guidance regarding UT Southwestern's IRB submission process for research materials that will be utilized to promote a study, reach out to the HRPP at HRPP@UTSouthwestern.edu.

Additional CMPA policies, guidance and training information are located on the CMPA website at Office of Communications, Marketing, and Public Affairs – UT Southwestern, Dallas, TX.

Finally, the Brand Identity Group, within CMPA, provides helpful guides and downloads to ensure that the UT Southwestern logo, colors, and typography are consistent as well as instantly recognizable wherever they may appear. Go to the following to download Brand Identity group approved PowerPoint templates, logos, brands, so forth: Our Brand ... and You | UT Southwestern Medical Center (utswmed.org). You will be required to enter your login credentials to access this website since this information is proprietary.

G. UTSW Policies

UT Southwestern supports a highly structured and regulated environment for the conduct of safe clinical research practices. The investigator and the members of the research team are required to follow all UTSW policies and procedures when conducting research within UT Southwestern, These policies also apply to students, providers, volunteers, and staff.

Overall Guidelines

UT Southwestern's policies can be accessed through the UT Southwestern Policies webpage https://www.utsouthwestern.net/intranet/administration/policies/. Access to the internal policies intranet is restricted and VPN login credentials are required in order to access these policies. The following is a list of important UT Southwestern policies that commonly apply to clinical research; however, this is not an exhaustive list.

Please note: printed policies may have been updated – ALWAYS VIEW CURRENT VERSIONS ONLINE.

- **RES-151 HUMAN RESEARCH PROTECTION PROGRAM**

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 UTSW, prior to the initiation of such research, "Subjects research conducted on behalf of UT Southwestern must not be undertaken or participated in by UT Southwestern faculty, staff, or students unless it has received prior IRB approval."

- **Privacy Policies**

There are numerous privacy policies that govern the research activities at UT Southwestern, such as compliance, consent for use and disclosure of PHI, de-identification and re-identification, limited data sets, and so forth. All of these policies are located in one central location.

- **FDA Letter of Non-Repudiation**

This letter from UT Southwestern's Chief Information Officer (CIO) to the US FDA attests that under 21 CFR Part 11, all electronic signatures executed by UT Southwestern's employees, agents, or representatives are the "legally binding equivalent of traditional handwritten signatures."

- **The Handbook of Institutional Policies and Operating Procedures**

The handbook contains the official policies and guiding principles established for UT Southwestern Medical Center. The scope of each policy indicates to whom and under what circumstances the policy applies. All individuals indicated in the scope must abide by the rules and regulations included in the Handbook. The Policy Handbook defines a statement and expectation that governs the standard principles of UT Southwestern and the expected behavior of those affiliated with, doing business with, or visiting the Medical Center. The above link provides access to the entire policy library as well as the ability to browse by subject topic.

The following chapters are notable for their impact on research practices:

- Chapter 2 – Administration (ADM)
- Chapter 3 – Ethics, Compliance, and Standards of Behavior (ETH)
- Chapter 5 – Environmental Health & Safety (EHS)
- Chapter 12 – Research (RES)
- Chapter 14 – Health System (HSO)

- **The UT Southwestern Policy Library**

The UT Southwestern Policy Library contains *The Handbook of Institutional Policies and Operating Procedures* (link directly above) and hospital-wide and ambulatory administration policies. It also includes departmental policies and standard operating procedures (SOPs) for the Animal Resource Center, and procedures, forms, and records for hospital-based clinical labs. Documents within the Policy Library represents the single source of truth for UT Southwestern institutional policies.

- **UH Pharmacy Policy and Procedures: Research**

This link will take you to a shared drive for the Pharmacy Policy and Procedure Manual and includes all Department Standard Operating Procedures (SOPs) that applies to research activities.

The following is a listing ***of just a few*** of the many SOPs included:

- Pharmacy Services Policy 11-004 Investigational Product: Inventory, Ordering, and Receiving
- Pharmacy Services Policy 11-005 Storage and Security of Investigational Products
- Pharmacy Services Policy 11-006 Drug Storage Temperature Monitoring
- Pharmacy Services Policy 11-007 Investigational Drug Accountability
- Pharmacy Services Policy 11-010 Site to Site Transfer of Investigational Drugs
- Pharmacy Services Policy 11-011 Destruction Disposal of Investigational Drug
- Pharmacy Services Policy 11-019 Drug Recalls

These SOPs apply to all individuals engaging in clinical research that involves dispensing or administering IP or study drugs to research participants on UT Southwestern premises, including the University Hospital and Hospital-Based Clinics, Ambulatory Clinics, the Clinical Research Unit, and all other locations or sites where clinical research is being conducted.

- **HRPP 1.5: 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. This policy and procedure applies to the Human Research Protection Program Department (HRPPD), affiliated institutions, and other Committees and Offices at UT

Southwestern which are integral to the review and oversight of human subjects' research.

For instance, any clinical research protocol that requires Institutional Biosafety Committee (IBC) approval will require submission and approval. IBC approval is required before final IRB approval may be issued. IBC approval is granted on a per protocol basis and NOT on a per agent basis. Therefore, each new submission, even utilizing an agent that had been previously approved under a separate protocol, will require re-review.

H. Additional Policies Related to Clinical Research

Organization	Policy #	Policy Title	Brief Description
UTSW	RES-151	Human Research Protections Program	Outlines the HRPP authority.
UTSW	RES-161	Use of Investigational Products and Study Drugs in Clinical Research	This policy applies to all individuals engaging in clinical research that involves dispensing or administering investigational products or study drugs to research participation.
UTSW	11-009	Dispensing Investigational Products	To ensure appropriate guidelines and safeguards exist to maximize patient safety, inform hospital personnel and involved medical staff of all aspects of investigational product (IP) use, in compliance with the study protocol and ensure any sponsor provided product is dispensed from the investigational drug services (IDS) pharmacy according to applicable regulations, sponsor requirements, and pharmacy policies.
UTSW	FSS-201	Records Management and Retention	UT Southwestern recognizes the need for orderly management and retrieval of its records and for a documented record retention and destruction schedule congruent with all state and federal laws and related regulations.
UTSW	HSO-253	Clinical Research Documentation in the Electronic Health Record	To ensure continuity of care, that healthcare providers can reasonably identify and contact research personnel, and that billing compliance documentation requirements are met, it is UT Southwestern policy that all clinical trial-related activities involving

			patients and participants in UT Southwestern-approved research study conducted on UT Southwestern premises must have sufficient documentation in the electronic health record.
UTSW	ADM-303	Requests for Information (Texas Public Information Act)	The Texas Public Information Act (TPIA), Texas Government Code §§ 552.001-.353, grants each person the right to request access to government information.
UTSW	ETH-201	Protection From Retaliation for Reporting Suspected Wrongdoing	Encourage employees to report (or cause to be reported) and to assist in UT Southwestern's investigation of any known or suspected improper activities or potential violations of laws, rules, policies, or regulations; and ▫Prohibit retaliation as a consequence of good faith actions in reporting or participating in investigations of allegations of misconduct or wrongdoing.
UTSW	UHLD 03	Product Review and Approval Process – Hospital Policy	This policy ensures that products and technology used in the provision of clinical care is safe and appropriately applied and managed. All new products, technology, or applications of existing products or technology should be approved by the Value Analysis Steering Committee (VASC) prior to scheduling patient intervention, whether for research, trial, or ongoing use. Procedures may not be scheduled and products may not be used without VASC approval. Staff should complete incident reports of any such items to allow investigation and follow-up.
COI	RES-401	Financial Conflicts of Interest in Research: Disclosure, Management, and Reporting	This policy describes the process by which conflicts of interest are reviewed by the Conflict of Interest (COI) Office assessed disclosures, and the COI Official and Committee review and manage identified conflicts.
COI	ETH-104	Conflicts of Interest, Conflicts of Commitment, and	This policy on conflicts of interest (COI), conflicts of commitment (COC), and outside activities provides the ethical guidelines for UT

		Outside Activities	Southwestern faculty and covered staff in these areas, and defines Covered Individuals.
COI	ETH-304	Institutional Conflicts of Interest	This policy on institutional conflict of interest (ICOI) describes the identification of ICOIs, defines the ICOI Committee, and management plans.
SPA	RES-153	Clinical Trials Billing Compliance	As a state agency and university, UT Southwestern has a responsibility to the public to promote an environment that ensures the highest standards of integrity in clinical research, patient billing, and all other associated activities.
OTD	INP-101	Technology Development and Intellectual Property Management	In accordance with the policies of the UT System Board of Regents and UT Southwestern, intellectual properties are commercially developed, and faculty and staff inventors are eligible for financial royalties resulting from the licensing of intellectual properties.

HRPP Specific Policies and Procedures

The following table lists all individual policies listed within the HRPP Policies and Procedures Manual. These policies, including additional resources, can also be accessed from the HRPP's website: HRPP Policies and Procedures: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX

Policy #	Policy Title	Brief Description
0.0	About the Human Research Protection Program	The University of Texas Southwestern Medical Center has assured the US Department of Health and Human Services (DHHS) of compliance with DHHS regulations (45 CFR § 46.103) for the protection of human subjects, through an Office of Human Research Protection (OHRP) approved Federalwide Assurance (FWA00005087).
1.1	Receiving, Routing, and Administrative Review of IRB Submissions	All exempt and non-exempt research submissions are submitted in the electronic IRB application system (eIRB). Submissions are routed to appropriate HRPPD staff and processed by HRPPDD staff in preparation for administrative review, expedited review, or convened IRB review. UT Southwestern IRBs maintain a system of HRPPDD pre-review and scientific & ethical prereview (as applicable) prior to the review by the expedited reviewer or

		convened IRB (see 2.1. INITIAL REVIEW OF RESEARCH)
1.2	Determining Whether an Activity is Research Involving Human Subjects	In accordance with federal and institutional regulations and prior to project implementation, the IRB must approve any undertaking in which a UT Southwestern faculty, staff, or student (i.e., an employee or agent) conducts non-exempt human research on behalf of UT Southwestern.
1.3	Exempt Review of Research	Research that meets the categories set forth by the federal regulations [45 CFR 46.104(d); 21 CFR 56.104(d); 32 CFR 219.101(b)] may qualify for exemption. This procedure documents the requirements for determining an exemption from human subjects research regulations
1.4	Study Closure and Inactivation	All studies that were previously approved by the UT Southwestern IRB or an external IRB should be inactivated upon completion of the study.
1.5	Communication with Other Committees and Offices	The Human Research Protection Program Department (HRPPD) and other organizational components integral to the Human Research Protection Program (HRPPD) will establish working relations to coordinate research protection related activities within UT Southwestern.
1.6	Reliance on Non-UTSW IRB	UT Southwestern investigators frequently collaborate in research involving external investigators and institutions.
2.1	Initial Review of Research	The IRBs must receive sufficient information from investigators to provide adequate review of proposed research and to make the determinations required by regulations for IRB approval. This policy describes the submission requirements and initial review process for research requiring IRB review.
2.2	Continuing Review of Research	The Institutional Review Board (IRB) conducts substantive and meaningful continuation review at intervals appropriate to the degree of risk. The research protocol must continue to satisfy the criteria set forth in 45 CFR 46.111 or 21 CFR 56.111 for the IRB to approve the protocol for continuation.
2.3	Modifications to Research	This procedure outlines the responsibilities of the investigator, IRB, HRPPD for the review of modifications to research previously approved by the IRB.
2.4	DOD Research	The PI is responsible for identifying DoD component requirements specified in the grant application guidelines and for advising the HRPPD staff and IRB of the requirements.

2.5	Exception From Informed Consent for Planned Emergency Research	The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24.
2.6	Research Involving Individuals with Diminished Autonomous Decision-Making Capacity	The Institutional Review Board (IRB) gives special consideration to protecting the rights and welfare of individuals with diminished autonomous decision-making capacity (DADMC).
2.7	Exception from Informed Consent Guidance	The objective of this guidance document is to assist investigators in planning, and the IRB in reviewing, protocols meeting the requirements for research that is designed for life-threatening, emergency situations, including the requirements that must be met for exception from, or waiver of applicability of, informed consent in these situations.
2.8	Collaborative Research Involving External Investigators/ Institutions Reviewed by UTSW IRB	UT Southwestern investigators frequently collaborate in research involving external investigators and institutions.
2.9	Repository	This policy applies to human subject research repositories established for the purpose of storing data and/or human biospecimens for future research purposes. This policy does not apply to data/human biospecimens that are collected and stored solely as part of routine clinical care or hospital procedures, such as blood banks, pathology, surveillance, or quality assurance. However, it does apply to data/human biospecimens from these sources that are then stored for future research.
3.1	Informed Consent Requirements	Obtaining legally effective informed consent of individuals before involving them in research is one of the central protections provided in the regulations governing research. Informed consent in research i s founded on the Belmont Principle “respect for persons”
3.2	Informed Consent by Surrogate	This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct research on problems that are unique to persons who have impaired decision-making capacity.
3.3	Informed Consent Waivers and Alterations	The IRBs have the authority to approve a consent procedure that does not include, or which alters, some or all of the federally

		mandated elements of informed consent provided the approved procedure meets applicable federal regulations.
3.4	Informed Consent of Subjects with Limited English Proficiency	UT Southwestern Medical Center is located in a culturally diverse area. Investigators are encouraged to recruit and include all segments of the community in research, including individuals whose primary language is not English.
4.1	Identification and Recruitment	The method used to contact patients for potential participation in research studies will be described in the recruitment plan.
4.2	Guidance for Advertising to Research Subjects	UT Southwestern Institutional Review Board (IRB) interprets federal regulations and Institutional policy, in accordance with the interpretation of OHRP and FDA, to provide IRB authority and responsibility for review of study recruitment material, including advertisements.
5.1	Principal Investigator Responsibilities in the Conduct of Human Research	The purpose of this policy is to provide an outline of responsibilities of the principal investigator (PI) involved in the conduct of human subjects' research.
5.2	Research Education and Training	University of Texas Southwestern Medical Center has a comprehensive educational program that ensures that individuals involved in the conduct or oversight of exempt and/or non-exempt human subjects' research understand the ethical principles and regulatory requirements related to the protection of human subjects.
5.3	Financial Conflict of Interest Management	Faculty and staff engagement in relationships with outside entities is not in principle unacceptable, and commercialization activities can align with the university's missions, but in practice, such interactions must be carefully managed.
6.1	Appointment and Evaluation of IRB Members and Chairs	This policy describes the regulations and requirements for establishing, maintaining and utilizing IRBs at UT Southwestern.
6.2	IRB Approval of Research	This policy and procedure sets forth the human research approval criteria for the IRB and the procedures for the approval of research process.
6.3	Conduct of Full Board Meetings	The UTSW IRB conducts convened meetings in accordance with applicable federal requirements for full review.
6.4	IRB Member and Consultant Conflict of Interest	Conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated

7.1	Drug Research Policy and Procedure	The IRB reviews projects that involve drugs or biologics to protect the rights and welfare of human subjects involved in such research/investigations as directed by the Department of Health and Human Services (DHHS) and by the Food and Drug Administration (FDA).
7.2	Device Research	The IRB reviews projects that involve medical devices to protect the rights and welfare of human subjects involved in such research/investigations as directed by the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA).
7.3	Humanitarian Use Device (HUD)	UT Southwestern IRB recognizes humanitarian device exemption (HDE) approval by the FDA is based on safety and probable benefit of a designated Humanitarian Use Device (HUD). All uses of a HUD require IRB approval.
7.4	Expanded Access Treatment Use of an Unapproved Drug/Biologic	This policy describes the procedures for utilizing the Food and Drug Administration (FDA) Expanded Access Program (EAP) including individual patient and intermediate or large population treatment investigational new drug (IND) applications.
7.5	Emergency Use of an Investigational Drug or Device	This policy is intended to assist physicians by outlining the FDA emergency use requirements and the necessary procedures to ensure both the treatment of seriously ill patients in a life-threatening situation and compliance with FDA regulatory requirements.
8.1	IRB Minutes	This procedure outlines the responsibilities of the Human Research Protection Program Department (HRPPD) and the IRB for documentation of convened IRB proceedings according to applicable regulations.
8.2	Reporting Policy and Procedure	This policy and procedures outlines specific actions and responsibilities of the Principal Investigator (PI), HRPPD and convened IRB's for ensuring prompt reporting of required activities, circumstances and results involving the conduct and monitoring of research involving human subjects.
8.3	Recordkeeping	This policy describes documentation requirements, storage and maintenance of records for the HRPPD.
9.1	Complaints	The purpose of this policy and procedure is to document the responsibilities of the Human Research Protection Program Department (HRPPD), the Institutional Official, the convened IRBs, Principal Investigators (PIs), and UT Southwestern employees for handling complaints regarding research.
9.2	UPIRSO and UADE	Prompt reporting to the reviewing IRB (and UTSW HRPP for reliance studies) is required for any unanticipated problems involving risks to

		subjects or others (UPIRSO) or unanticipated adverse device effects (UADE).
9.3	Noncompliance Review	This policy outlines responsibilities for managing issues of noncompliance with human subjects regulations, IRB requirements, institutional policies, or IRB determinations.
9.4	Suspension or Termination of Research	The convened IRB or Institutional Official (IO) may suspend or terminate approval of research that is not being conducted in accordance with the IRB requirements or that has been associated with unexpected serious harm to participants.
9.5	Reportable Events (RE) Guidance	This reportable event guidance applies to all non-exempt research conducted by or on behalf of UT Southwestern (UTSW), its affiliates, and investigators, sites, or institutions relying on the UTSW IRB.
9.6	ClinicalTrials.gov Requirements	UT Southwestern Medical Center is committed to fostering compliance with requirements concerning the public availability of clinical trial data on ClinicalTrials.gov.
10.0	Glossary of Human Research Terms	Access this searchable PDF to locate definitions as acknowledged by the Human Research Protection Program Department.

I. Additional Entities Researchers Should Be Aware Of:

Sponsored Programs Administration (SPA)

Sponsored Programs Administration is the central department that assists UT Southwestern researchers by facilitating proper stewardship of industry funds. SPA helps principal investigators and study teams complete Medicare Coverage Analysis, negotiate industry agreements, and manage payments for subjects participating in clinical trials.

Once you establish a relationship with a sponsor for your clinical trial or patient treatment and have an agreement in place – you must submit the contract terms to Sponsored Programs Administration (SPA) for review and negotiations through eAgreements.

Please note:

- SPA manages the negotiation of clinical research industry and clinical and nonclinical non-industry research agreements.
- Department is not authorized to negotiate terms on behalf of the institution.
- A UT Southwestern official, such as Human Research Protection Program (HRPP), Institutional Review Board (IRB), or SPA, must sign the agreement indicating their

consent to the contract terms. Otherwise, the agreement is not valid.

A Clinical Trial Agreement is a contract between the University and a sponsor for funding and executing research at UT Southwestern.

Types of Agreements

All agreements start with your department and must route to SPA, where it will be assigned to a Contract Specialist.

- **Industry Agreements**
  Funded by an industry sponsor
- **Non-Industry Agreements**
  Funded by the state, federal government, private organization, or foundation
- **Personal Agreements**
  Funded by an outside entity who has a direct relationship with a UT Southwestern employee. These agreements are handled by the Conflict of Interest Office.

eAgreements Review Process

Your agreement will undergo internal review. The following details each stage of the assessment process.

- **Pre-submission**: The agreement has been entered, but it has not been submitted by the Department.
- **Unassigned**: The agreement has been submitted, but it has not been assigned to a specialist.
- **Internal Review**: Internal SPA team is working on reviewing the agreement terms.
- **External Review**: The agreement is with external sponsor pending external review.
- **Clarification Requested**: The agreement is with the department pending requested information.
- **Routing for Signatures**: The agreement is routing for signatures both, internally and externally.
- **On Hold**: The agreement is on hold.
- **Withdrawn**: The agreement is currently withdrawn, pending final items and must be resubmitted by the Department.
- **Active/Approved**: The agreement has been fully executed.

Coverage Analysis (CA) is a systematic review that examines clinical trial protocols and determines the items and services to be billed to the study sponsor or the insurance company.

Please adhere to the following steps for the Coverage Analysis of your study. These tasks may be completed in parallel when appropriate:

- Manage all updates and results on clinicaltrials.gov
- Register your study in Velos
- Register your study with IRB
- Request a Coverage Analysis from SPA's Coverage Analysis
- Review Coverage Analysis and request changes if applicable
- Negotiate your final budget with sponsor
- Approve Coverage Analysis in DocuSign
- Approve Coverage Analysis modifications in DocuSign, if applicable

You can submit your Coverage Analysis (CA) documents through the Velos system once your IRB application is complete or in draft. To begin the CA process, submit the following required documents:

- Protocol
- Consent draft
- Budget draft, if available
- Investigational New Drug (IND) letter, if applicable
- Investigational Device Exemption IDE letter, if applicable
- Centers for Medicare & Medicaid Services (CMS) IDE approval letter, if billing to Medicare will be done on a research device
- ClinicalTrials.gov Registration Number (NCT) number
- IRB application draft
- Complete Performance Site Review form (PSF)
- Once the coverage analysis draft is available in Velos, you can locate the draft under the **Documents tab in Velos**
- Departmentally funded studies - Chart of Account (COA) should be added to the Velos Summary tab

You can submit your contract through the eAgreements system simultaneously as the IRB full or partial application is completed. However, you may submit a contract review request before submitting your IRB application.

For step-by-step assistance with submission of your agreement, by contract type, please reference the submission guides on the SPA website.

To begin the contract review process, submit the following required documents:

- Sponsor agreement template draft
- Coverage analysis draft submitted in Velos
- Consent document draft (either in eAgreements or eIRB)
- Protocol draft (either in eAgreements or eIRB)
- Budget draft (final budget if Statement of Work (SOW) is being submitted)
- IRB application draft

All industry and non-industry agreements must route through SPA's internal review process for approval or institutional endorsement before you can start the award setup process.

Your clinical research project entails essential details for SPA to produce an award ID number and execute an agreement. These attributes are system requirements to properly administer, invoice, and manage payments for your project.

Examples of Required Award Details

- Sponsor Name
- Recipient/Awardee
- Expected Amount of Funding per Patient (Based on Contract)
- Effective Date of Performance
- Terms and Conditions

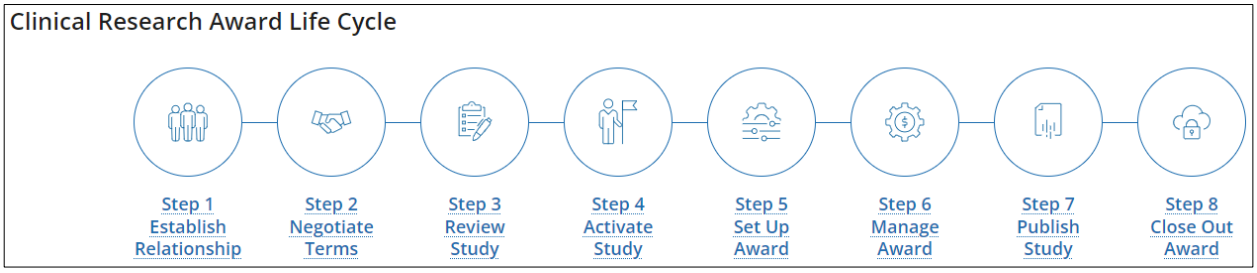
As a recipient of federal funds, SPA ensures that UT Southwestern projects remain compliant with all regulations, such as under Medicare. Per Medicare regulations, UTSW providers:

- 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

For information regarding research billing and compliance, please go to the following: https://www.utsouthwestern.edu/employees/spa/

Within SPA the major responsibilities listed above are further sub-divided into specialized offices that oversee its management: Central Coverage Analysis Group (CCAG), the Clinical Trial Finance Team, and Grants, among others.



The **Central Coverage Analysis Group (CCAG)** performs a systematic review of protocol-related documents to determine if all patient care costs in a study are covered by the study sponsor, other funding sources, or qualify for reimbursement by third party payers, such as Medicare. The team completes a coverage analysis for all clinical research studies (including clinical trials) that involve billable procedures.

The **Clinical Trial Finance Team** is responsible for the billing and invoicing of clinical trials, in conjunction with departmental personnel. Additionally, the CT Finance Team handles clinical trial budget review, ClinCard administration, treasury services for all awards, On Account payment management, customer maintenance, bank account validations, and management of Payment Management System (PMS) draws.

Sponsored Programs Administration is the central department that assists researchers with applying for funding and managing their awards. SPA helps Principal Investigators and

departments submit research proposals, execute grants, contracts, cooperative agreements, and fiscally manage sponsored awards and agreements. The Grants office within SPA provides support to study teams throughout the lifecycle of their grant support, as follows:

The Pre-Award stage refers to identification of a funding opportunity, development of a proposal, and submission of the proposal to the sponsor for review. Pre-Award is composed of two teams; Proposals and Non-Industry Agreements. Pre-Award reviews proposals/agreements, assists with required updates/changes, and submits proposals/agreements to sponsors for funding.

The Post-Award stage encompasses grants management activities after an award is received. Post Award is composed of several teams: Award Setup, Award Maintenance, Revenue Cycle, SPA Cash Management, Financial Reporting and Award Close-Out. Post Award manages the financial aspect of research funding from making funds available to spend, performing billing & invoicing functions, completing award modifications, submitting financial reports, and closing out projects in compliance with regulatory requirements.

Additional tools and resources can be found on the SPA website: https://www.utsouthwestern.edu/employees/spa/tools/

Answers to clinical research frequently asked questions can be found on the SPA website: https://www.utsouthwestern.edu/employees/spa/faqs/clinical/

SPA offers comprehensive training modules available in Taleo Learn: https://www.utsouthwestern.edu/employees/spa/education/

Office of Clinical Research (OCR)

The Office of Clinical Research (OCR) oversees the conduct of clinical research holistically and promotes flexibility, creativity, efficiency, and responsiveness.

The OCR's focus is on collaboration and how to best harness the collective resources of UT Southwestern Medical School, UT Southwestern hospitals and ambulatory facilities, and the many UT Southwestern affiliates such as Parkland, Children's, and Texas Health Resources to advance clinical research to help patients. The OCR acts as a liaison for clinical researchers to obtain support and receive services within and outside the institution for successful conduct of clinical research. It brings together all programs and facilities, so researchers have a centralized place to access all resources. OCR's key areas of oversight include the following:

Workforce:

- New career paths, market analysis of compensation, recruitment, and retention efforts (Human Resources (HR)
- Develop and disseminate curriculum and educational series for faculty and staff (Education and Training)
- Provide seed funding and scholarships to promote clinical research (Clinical Scholars)

Information Technology (IT):

- Clinical research IT resource planning, management, and enhancement in collaboration with Research Academic Systems

Clinical Research Finance:

- Research billing review and compliance
- Track clinical research financial performance and optimize revenue recovery

Infrastructure and collaborations:

- Promote new scientific collaborations and opportunities for clinical research
- Increase new trial opportunities, and strengthen data science and implementation research domains
- Establish and/or enhance infrastructure (ex: facilities, personnel, databases, bioinformatics, and biostatistics)

In order to achieve the key areas of oversight mentioned above, services provided by the OCR include, but are not limited to:

- Research Staff Training
- Credentialing, and Participant Recruitment
- Aston Clinical Research Unit (CRU)
- Research Billing Review (RBR)

- Institutional approval through the Office of Clinical Trial Management (OCTM)

The **Research Staff Training** office within the OCR supports staff training on basic research skills, organizational optional polices, and government regulations. They also provide training recourse and collaborates with departments to create clinical research courses to facilitate on-going research initiatives. Send all questions to the OCR inbox.

The **Research Participant Recruitment** team within the OCR works with study teams to develop and implement innovative recruitment strategies to recruit research participants. More detailed information about the Research Participant Recruitment team's services is outlined under Chapter 11, General Support Services. To request a research recruitment consultation, click here: Book.

The **Aston Clinical Research Unit (CRU)** within the OCR is a fee-for-service, institutional resource designed to support the safe and ethical conduct of research while enhancing the research experience for study participants. More information about the CRU is under Chapter 11, General Support Services.

The **Research Billing Review (RBR)** process within the OCR is designed for clinical research billing compliance. Linking patients to their research patient timeline and encounter(s) is a critical process for research billing compliance as it determines who is going to be billed – Research (study sponsor), or Routine Standard of Care (insurance/patient).

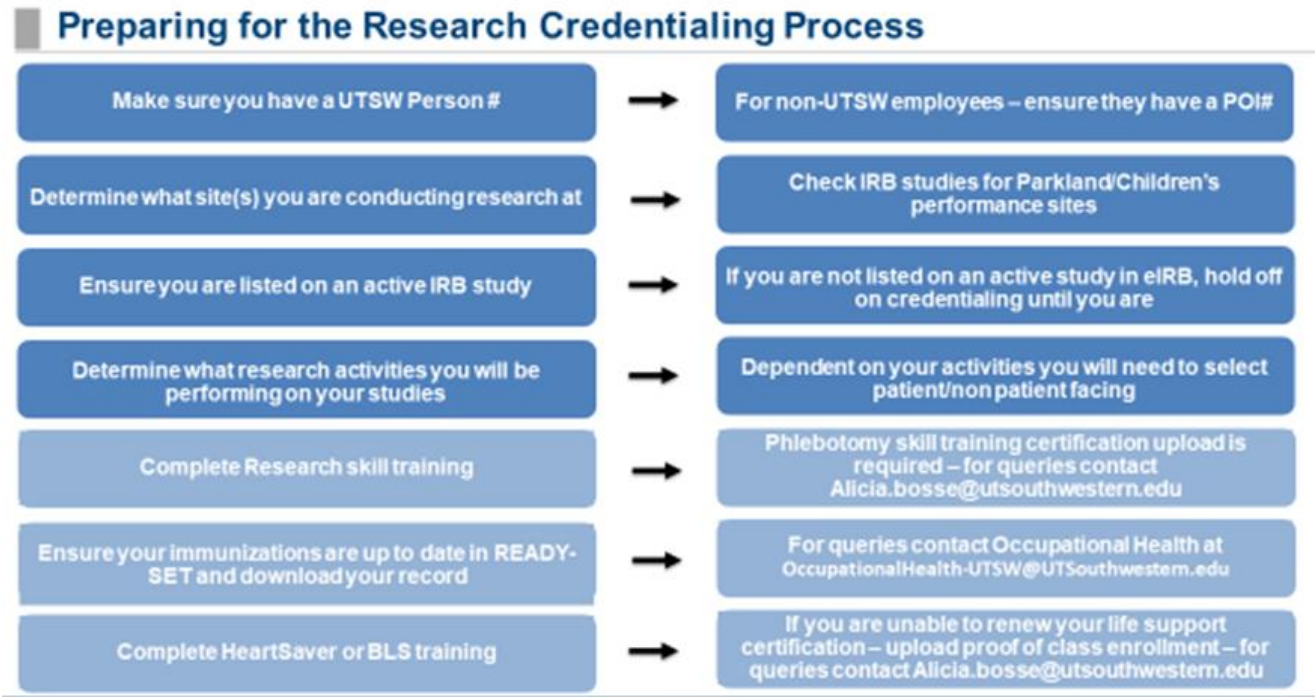
For information on how to link a patient encounter to research billing, understand more about VELOS (which has implications for RBR depending on what statuses you select for patients in the system), as well as other topics covered by the RBR, please go to: Research Billing Review (RBR) – Office of Clinical Research (utsouthwestern.net).

For additional information on the OCR, or to request a consultation, please go to Office of Clinical Research – MyUTSW (utsouthwestern.net) or go to Clinical Research – UT Southwestern, Dallas, Texas

Research Staff Credentialing Office

The **Research Staff Credentialing Office** within the OCR conducts credentialing on research staff conducting activities at UT Southwestern and initiates credentialing for individuals completing research at Parkland. Individuals named on a study must complete the credentialing process if they are not already credentialed through either the Medical Staff Office (MSO), Graduate Medical

Education (GME) or through the Nursing Office. The requested information includes basic demographics, information regarding life support certifications, Occupational Health status, study information, professional licenses, and competency verifications (phlebotomy, EKG, and/or blood pressure checks).



The credentialing process is conducted at hire or at the time of study Involvement, and it is repeated annually. Timely completion is necessary to prevent suspension of access at both UT Southwestern and Parkland. Credentialing materials should be submitted when all information is complete (please do NOT submit without all requested information. This will delay your credentialing).

To initiate this process, email the Research Credentialing Office. There is also additional information, including tips and tricks, shared in the FAQs section (under Chapter 11).

Office of Clinical Trial Management (OCTM)

The **Office of Clinical Trial Management (OCTM)** within the OCR ensures that the sites at which the clinical research will be performed are able to comply with the safe and compliant conduct of the clinical trial. The OCTM ensures that UT Southwestern – as a performance site (PS) at which the clinical research will be performed – is:

- able to comply with protocol and regulatory requirements
- has the technical, operational, equipment, infrastructure, and staff required

A UTSW Performance Site Request Form (PSRF) should be completed for all studies that lists UTSW as a Performance Site in eIRB. This includes:

- All studies being conducted at a UTSW-owned facility
- Chart Reviews/Registries/Data Collection and Analysis studies which involve UTSW data
- Studies where only the PI or the study staff is UTSW employed, and all other research procedures are done outside of UTSW

The PSRF will be submitted to the OCTM when the study's eIRB status is updated to "Awaiting Assignment." When the study is Approved in eIRB, the Principal Investigator and the Primary Research Coordinator listed in Velos will receive email notifications regarding the Performance Site status updates.

The following provides an overview of important concepts, definitions, and tips on working with PSRFs. For additional questions please contact: OCTM@UTSouthwestern.edu.

UTSW PSRF Components: Study Type

There are three categories of studies that are added to Velos and go through the review process by OCTM, which includes verification of UTSW research credentialing. NOTE: Research Credentialing check is the first step in the UTSW PS review. **Please ensure all your research staff have active UTSW research credentialing before submitting your PSRF.**

1. **Complexity 0**: Research staff employed by UTSW, but all study activities occur entirely at other affiliated institutions. UTSW performance site approval is not required, but an approval from affiliated institutions like Childrens, Parkland, etc.is necessary for Greenlight activation.
    - UTSW PS Approval Status will be marked in eIRB as "Not Applicable" followed by approval by the affiliated institution necessary for Greenlight activation
2. **Complexity 1**: Studies conducted by UTSW staff at UTSW, but do not involve the use of any UTSW facilities by research participants (this includes Chart Reviews, Online Surveys and Questionnaires, Testing at Health Fairs, etc.)
    - Review the Research Credentialing of ALL study staff
    - Confirm no on-site in person activities occur
    - UTSW PS Approval issued and feeds into the Greenlight progress
3. **Complexity 2**: All studies which involved any interaction with human participants in a UTSW-owned facility (such as a hospital, clinic, lab, etc.)

- UTSW PS Approval issued and feeds into the Greenlight progress
- Current research credentialing is required for all non-physician research staff who will have contact with PHI
- MDs and Dos credentialed to practice at UT Southwestern do not need to complete a separate research credentialing at UTSW

UTSW PSRF Components: Locations

- List detailed locations where any of the study activities will occur, by specific locale on campus. For example, CUH 7N inpatient unit; General internal medicine clinic; CUH ER, CRU- Aston; CRU- Sprague; Zale Inpatient Research Room; Zale Inpatient research Room; CUH Hospital; ZL- Outpatient PM&R; CC- Fort Worth; Surgery clinic Richardson
- If AIRC is checked in the form, then please fill out the AIRC form
- If any activity is also performed outside of UTSW, please complete the respective performance site form for that facility (e.g., Childrens, Parkland, etc. More on the performance site requirements for these entities are available in **Section J. Affiliated Hospitals**)

UTSW PSRF Component: Procedures

- List only the procedures being done for research
- Please do not list procedures which are considered Standard of Care
  Note: Do not list radiology and laboratory tests as those will be collected in separate sections. Examples of procedures to be listed in this section include EKG, echocardiogram, pulmonary function test, oral glucose tolerance test, inpatient hospitalization for observation, ophthalmology examination, etc.

UTSW PSRF Study Status Notification Categories:

- ***Incomplete*** – OCTM has received site request, but research credentials have not been completed for study team members or missing information needed on the form. Study team must resubmit the request for performance site review under 'study status' tab to notify OCTM
- ***Approval Not Required*** – All study related activities are conducted at an affiliated institution. For Greenlight activation, study must be approved by the affiliated site.
- ***Approved*** – Study is approved. No further action is needed.
- ***Disapproved*** – OCTM has not received any response from study team on their study >45 days or study has been withdrawn from IRB. Study teams need to resubmit Performance

Site form and email octm@utsouthwestern.edu to restart review process.

- ***On Hold*** – OCTM has reviewed the study but there are one or more issues remaining. Please check notes in Velos. Ex. CLS pricing or credentialing confirmation.
- ***Pending Review*** – OCTM has received the site request. Performance Site is under review, and study may be taken to meeting; no further action is needed. Status will be updated when approved.

UTSW Performance Site Approval Letter: Important Reminders:

- *UTSW Performance Site Letter of Approval provides approval for locations, research only procedures and services for the study*
- *Approval is contingent upon compliance with UT Southwestern IRB rules and regulations and all applicable institutional policies*
- *Studies occurring at Children's and Parkland should complete each respective Institutions Site Approval*
- *Uploaded in Velos under the Documents Section*

Additional Helpful Hints from the OCTM:

- Study Status can be viewed in the Study Status tab in Velos. If your study is not approved, it is most likely due to a pending ancillary approval.
- OCTM DOES NOT receive a notification that a message has been left by the research team in the Notes section of the Study Status tab. Please email the OCTM team member directly or via the general inbox at OCTM@UTSouthwestern.edu to convey information.
- "UTSW" must be selected as a site in Velos ***AND*** eIRB's section 5.0 in order for the OCTM to review your study.
- If you are receiving a notification to complete the UTSW PSR form, please make sure that you are completing the correct form: "UTSW Performance Site Review Form." This UTSW Performance Site Review Form is located in Velos under the Forms tab (i.e., the last Form in the drop-down menu). Once the Form is complete, ensure that the Form Status is set to "Completed" status and then submit the study.

For inquiries to the OCTM, contact the office with a General Inquiry email at OCTM@UTSouthwestern.edu. For more information about the affiliated hospitals that may also be listed as performance sites in clinical research, please visit **Section I. Affiliated Hospitals**.

Office for Technology Development (OTD)

The Office for Technology Development (OTD) assists UT Southwestern researchers by

cultivating collaborative relationships with both the public and private sectors for the purpose of protecting, enhancing, and advancing UT Southwestern innovations to maximize benefits for community health and well-being. OTD is responsible for a variety of contractual agreements and ensures that these agreements remain consistent with UT Southwestern' s mission as well as policy. The types of agreements handled by OTD include, but are not limited to, non- clinical related Confidential Disclosure Agreements, all incoming and outgoing Material Transfer Agreements, receiving Data Use Agreements, Sponsored Research Agreements, Collaboration Research Agreements and Visiting Scientist Agreements. OTD also manages and commercializes the intellectual property arising out of UT Southwestern's research endeavor through a variety of agreements, including but not limited to License Agreements, Option Agreements, Equity Agreements, and Inter-Institutional Agreements.

The agreements below are the responsibility of OTD. All require IRB approval:

- **Receiving Data Transfer Agreement (DTA)**. A DTA outlines the rights and obligations pertaining to the use, handling, protection and safeguarding of data being received. A DTA comprises the transfer of de-identified data only.
- **Receiving Data Use Agreement (DUA)**. A DUA establishes who is permitted to use and receive a Limited Data Set (LDS), and the permitted use and disclosure of such information by the recipient. A LDS is described as health information that excludes certain direct identifiers, but may include city; state; ZIP Code; elements of date; and other numbers, characteristics, or codes not listed as direct identifiers.
- Providing and Receiving **Material Transfer Agreements (MTA)** for human materials. A MTA is a contract with terms that govern the transfer of tangible research materials between two or more organizations (universities, non-profit entities, or for-profit entities). The MTA defines the rights of the provider and the recipient with respect to the materials.

Go to the following for more information about the OTD's services and/or to request assistance: Office for Technology Development – UT Southwestern, Dallas, Texas

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. Laboratory safety resources and requirements vary depending on the scope of the research being conducted. Moreover, training requirements can vary from person to person based on your

assigned scope of practice: Scope of Service for Healthcare Personnel in Clinical Research.pdf (sharepoint.com).

Contact the Ambulatory Clinical Education group within the Office of Clinical Research (OCR) if you are unsure what classes and/or training you are required to take: Ambulatory Clinical Education and Professional Development.

Office of Research Support and Regulatory Management (RSRM)

The Office of Research Support & Regulatory Management (RSRM) oversees components of basic and clinical research that aim to help investigators assure compliance with regulatory requirements and institutional policies.

The RSRM office is a centralized recourse that encompasses multiple units:

- Conflict of Interest (COI) and Conflict of Commitment (COC)
- Export Control (EC) and International Collaborations
- Institutional Animal Care and Use Committee (IACUC)
- Stem Cell Research Oversight (SCRO)

The RSRM office also supports multiple campus initiatives to assist our investigators in maintaining compliance with regulatory and institutional requirements. These include:

- NIH Data Management and Sharing (DMS) Policy Readiness – This resource is a **collaboration of multiple UTSW research administrative and support departments to ensure that PIs submitting new NIH applications are in compliance with the recently implemented NIH DMS policy.**

- Departing Researchers: Research Project and Data Checklist – This resource provides **contact information for those offices that should be notified when the departure of researchers leads research projects to be discontinued or transferred.**

In addition, the RSRM office provides support to the UT Southwestern Medical Center CTSA Program. Particularly, our office manages the CTSA H1 Core which is a collaborative effort between the Texas A&M School of Veterinary Medicine & Biomedical Sciences and the University of Texas Southwestern Medical Center. The intent of the Core is to facilitate cross institutional research partnerships to promote the development of translational research models leading to novel therapeutics and diagnostics.

The **Conflict of Interest (COI) Office**, part of the Office of Research Support and Regulatory Management, oversees the identification, management, and monitoring of conflicts of interest and conflicts of commitment, and the approval of outside activities. Conflict of interest (COI) and conflict of commitment (COC) refer to situations where one's secondary interests (such as personal financial interests or outside activities) could impact one's primary interests (UTSW research, institutional responsibilities, etc.). The COI Office, and COI Committee, address both of these.

All outside activities and personal financial interests, and those of covered family members, must be disclosed in one's COI Statement of Financial Interests annually and within 30 days of any changes. Statements must be submitted regardless of whether there are items to report. Completed COI Training and submitted COI Statement of Financial Interests for all investigators and research staff are required for all IRB protocols and research grant applications.

The COI Office identifies conflicts of interest, conflicts of commitment, and requests supervisor approval for outside activities. The COI Office facilitates requesting supervisor approval and documents this according to Policy. The COI Office reviews the content of all submissions and identifies any conflicts. COIs are reviewed and managed via a Management Plan issued by the COI Committee.

COIs and COCs may occur in connection with research or institutional responsibilities, as well as other reasons. While many COIs are due to the confluence of research at UTSW and outside activities with a sponsor or manufacturer, there are infinite ways a COI or COC may appear. The UTSW COI Office is not limited to identifying conflicts with clinical research involving human participants; for example, we may identify and manage conflicts that involve retrospective chart review, de-identified data analysis, basis research, and other conflicts.

Conflicts are not inherently "bad", and many can be successfully managed by the COI Committee. Strategies to manage COIs should not be implemented without first discussing them with the COI Office.

The Export Control Office ensures UTSW's ongoing compliance with United States Government's export control regulations. If an international component is present, there is an export control consideration. Export Control (EC) and International Collaborations refers to the regulatory responsibility to ensure that international items, technology, software, IP, and collaborations meet relevant export control requirements. The EC Office performs risk assessments for international

shipments, travel, research funding, the Export Control portion of visa applications, vendors, and international collaborations.

Export Control regulations are complex. These regulations are set by three primary federal agencies with the ability to lobby heavy fines and restrict future exports. These agencies classify goods, identify restricted parties and destinations, and apply sanctions to support international trade compliance, economic objectives, and national security interests. Most research at UTSW is considered "low risk," and can quickly be assessed, but when Export Control concerns are present, the primary objective is always complying with the regulations.

Export Control is universally applied. Every activity, research project, award, and publication with an international component is subject to Export Control risk assessment. Therefore, proactively reaching out to Export Control with requests for assessment of any planned international components will help ensure that you are informed, and any Export Control concern can be addressed.

All research projects conducted by UTSW investigators involving live vertebrate animals require prior review and approval by the Institutional Animal Care and Use Committee (IACUC). The committee members oversee the welfare and humane care of animal research subjects.

The Stem Cell Research Oversight (SCRO) committee oversees research and reviews activities involving human embryos, human embryonic stem cells (hESCs), and human induced pluripotent stem (iPSCs). Additional information about the SCRO Committee is located in Chapter 2, Section E: Ancillary Review Committees.

The RSRM Office can be reached at 214-648-0456 (or ext. 8-0456 if you are on campus) to speak to someone live or leave a message. More information about the RSRM and its units can be found here: https://www.utsouthwestern.net/intranet/research/rsrm/

J. Affiliated Hospitals

UT Southwestern is world-renowned for its research and the quality of clinical care its faculty provides to patients at UT Southwestern University Hospitals & clinics ***and affiliated hospitals***. UT Southwestern Faculty physicians offer patient care at UT Southwestern University, Hospitals & Clinics, Parkland Health & Hospital System, Children's Medical Center, Texas Health Care System, and other affiliated hospitals and clinics.

Each of the hospitals listed below outline a brief overview of their services and resources, with an emphasis on research operations. Whenever an affiliated hospital is listed in a research study application as a performance site, performance site approval must be obtained ***prior*** to beginning enrollment at the site. This is because Human research studies proposed to occur at UT Southwestern Medical Center or one of the affiliated performance sites require each site's individual approval before any research-related activities can initiate at that site. In terms of a real-world example, if your study lists both UTSW and Parkland as performance sites but has only received IRB approval from the OCTM for UTSW, then the study may only screen, consent, and enroll UTSW patients until Parkland grants their performance site approval. Moreover, all scientific publications based on research studies that involve a non-UTSW performance site must acknowledge the contributions of the partner site(s).

For additional guidance on the performance site approval process with UT Southwestern's affiliated hospitals, as well as access to documents that the outline conditions and wording for affiliated site acknowledgements in research publications, please review: Performance Site Review: HRPP – UT Southwestern, Dallas, TX. This website also contains the Site-Specific contacts for each institution.

Parkland Health and Hospital System

Dallas County Hospital District d/b/a Parkland Health first opened its doors in 1894 and is now one of the largest public hospital systems in the country. Parkland is home to a Level 1 Trauma Center and a Burn Center, both of which are internationally recognized. Parkland is also home to the first Neonatal Intensive Care Unit (NICU) in Dallas County and has the largest Level III NICU in the region. The hospital is also known for its specialty medicine clinics for epilepsy treatment, arrhythmia management, and diagnostic cardiology, among others. Its emergency room is one of the busiest in the country. Parkland serves as a primary teaching site for UT Southwestern.

Parkland's Office of Research Administration (ORA) is responsible for promoting, supporting, strengthening, and growing the research infrastructure and support services at Parkland Health. Parkland and UT Southwestern are separate legal and operational entities that promote a collaborative research program outlined in the UTSW-Parkland Research Affiliation Agreement. Parkland holds a Federalwide Assurance with the Office of Human Research Protection, (OHRP), and has executed an IRB Reliance Agreement with UT Southwestern.

All research-related activity is routed through the ORA and may include the following:

- Grant opportunities, feasibility, and submissions
- Sponsored program activities
- Research-related agreements and contracts (including IRB reliance agreements, Data Use Agreements, Facility Use Agreements, Letters of Indemnification, etc.)
- Research compliance
- Clinical research services, including interface with support services (Radiology, Pathology, Pharmacy Investigational Drug Service, IT, Security, etc.)
- Data requests and extraction
- Study design and analytics consultation
- Research billing and finance
- Research credentialing for non-physician research staff
- Research-related training and troubleshooting

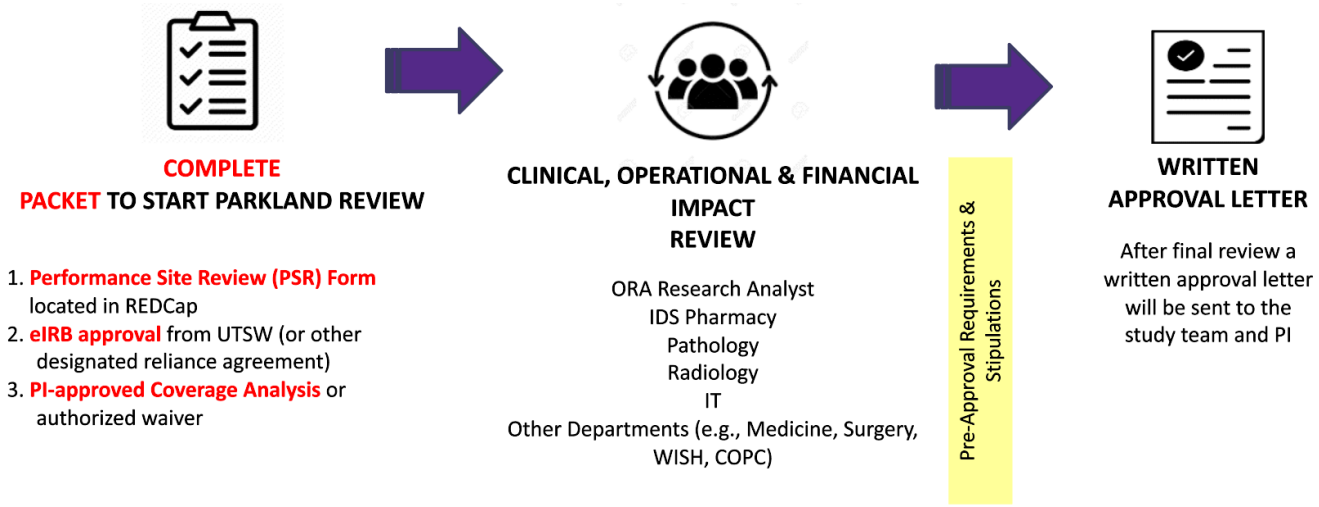
In accordance with the Research Affiliation Agreement, all research to be conducted at Parkland

or with Parkland data or resources must undergo review and approval by the ORA. The review and approval process identifies and works to facilitate the operational, financial, compliance and safety impact to Parkland.

Parkland's Performance Site Review process:

Proposed *research utilizing Parkland facilities, data or resources requires written Parkland site approval prior to starting any research activity.* A copy of the Parkland Researcher Handbook is distributed to all research coordinator staff and to all new study requestors. ORA offers monthly orientation sessions, on site tours of Parkland facilities, and coordination of Parkland Epic access and badge access.

The diagram below shows the process for submitting a study to Parkland:



<u>Pre-approval Requirements for initiating research at Parkland:</u>

The following lists all of the steps that need to occur in order for research activities to be approved at Parkland:

- IRB Approval (including fully translated consent, as applicable)
- Executed IRB Reliance agreement (as applicable)
- Approval from Parkland Departments (IDS pharmacy, pathology, IT, radiology)
- PI-approved orders sets in Parkland's Epic (for select studies)
- Documentation of education and or training with appropriate departments and staff
- PI-approved coverage analysis (with budget) or authorized waiver
- Executed contracts/legal agreements (LOI, DUA, FUA, as applicable)
- Executed Service Order Agreement (Parkland SOA = billing agreement)

- Research personnel coming to Parkland require initial and annual Research Credentialing (with skills check-off, and ORA-approved access to Parkland Epic, as applicable)

For more information, please contact:

Office of Research Administration

8435 N. Stemmons Fwy., 10th Floor, Dallas, TX 75247

PHONE: 214.590.1170

GENERAL INQUIRIES: Research@phhs.org

EXTERNAL website: https://www.parklandhealth.org/research

INTERNAL website: https://phhs.sharepoint.com/ResearchAdministration

Children's Research Administration was established in 2002 to provide support for the clinical and translational research conducted at Children's Health. With emphasis on maintaining high ethical standards and compliance with local, institutional, and federal regulations, Children's Health Research Administration's overarching role is to ensure that research at Children's Health is supportive of our patients, their families, and researchers across affiliated and non-partner organizations. Our mission is comprised of 9 primary areas and service roles:

1. **Administrative Oversight** – Our organizational core is responsible for the overarching management of the department and for providing support to the other primary areas. This includes the management and deployment of research support staff, fiscal management, contracts management, policy creation and management, internal funding, and all aspects of research operations. For more questions, please email: Research@childrens.com

2. **Research Support Staff** – We employ, train, and deploy Clinical Research Coordinators, Clinical Research Associates and Clinical Research Nurses across all clinical areas within Children's. They are trained in a wide array of research sub-specialties as well as in regulatory start-up and study close out; and are available to support clinical research across the institution on a short or long-term basis. For more questions, please email: Research@childrens.com

3. **Patient Advocacy** – Research Administration can offer the service of having a third-party person acting as a Patient/Family Advocate during informed consent and other phases of the project as needed. The Patient/Family Advocate acts with impartiality to ensure that the patient/family is treated fairly and that they understand the risks and benefits of study participation. For more questions, please email: Research@childrens.com

4. **Clinical Research Education** –To ensure compliance with institutional research policies, we offer initial and ongoing research education (e.g., Research 101 Faculty, Research 101 – Tier 1, Research 101 – Tier 2) to all personnel who conduct research at Children's Health. We also create research education tools, individualized training plans, and upon request, department-level training for medical students and fellows. For more questions, please email: Research.Education@childrens.com

5. **Research Finance** – Finance Team is comprised of professionals trained in finance, accounting, and business management. A part of their responsibilities includes maintenance of the research fee schedule, management of service order agreements (SOA), invoicing/billing for all research services performed on clinical trials, tracking research and grant expenditures, managing research revenue, and performing revenue allocations. For more questions, please email: Research.Finance@childrens.com

6. **Quality Specialists (QS) Team** – Our QS team provides internal oversight to all research protocols initiated at Children's Health by verifying credentialing, conducting performance site reviews, initiating and executing pricing agreements, and assisting with Children's Health site approval. They also assist research teams in the proper conduct of studies by performing quality reviews on research trials. For more questions: please e-mail: Research_Department@childrens.com

7. **Funding** – Children's Health has internal funding mechanisms to support innovative research ideas. Through our Mission and Service Package Grants, we also provide funding support for biostatistical needs, data pulls, and clinical research staff for meritorious PI-initiated projects. For more questions, please email: Research@childrens.com

8. **Statistical design & analysis** – Biostatisticians in Research Administration are available to provide statistical support and training to all members of the research community at Children's Health in the areas of study design, study implementation, analysis, and interpretation of the research data. For more questions, please email: Research@childrens.com.

9. **Grant Writing** – Children's Health offers assistance with writing grants and research proposals. Our Grant Writer works with investigators to plan, prepare, write, complete, and submit grants and research proposals. This resource is limited and is available on a first come, first served basis. For more questions, please email: Research@childrens.com.

Performance Site Review & Approval – Areas of Responsibility:

- Verification of IRB Approval
- Verification of IRB Reliance agreement (for studies under external IRB oversight)
- Approval from Children's Ancillary Service Departments (IDS pharmacy, Laboratory/Pathology, IT, and Radiology)

- Credentialing of Research Staff (Initial and Annual re-credentialing) or Attestation Statement
- Documentation of CMC required research training
- Pass thru review and approval of Advanced Analytics data requests
- Documentation of PI-approved clinical trial coverage analysis or authorized waiver
- Review and Verification of Patient Facing Documents (e.g., IC/Authorization) against study protocol
- Verification of MTA, DUA, LOI (as applicable)
- Executed contracts/legal agreements (FUA required for industry funded projects)
- Executed Service Order Agreement (SOA)/Scope of Work (SOW)

For more information, please contact:

Children's Health | W. W. Caruth, Jr. Center for Pediatric Translational Clinical Research

1935 Medical District Drive, Mail Stop F3.61, Dallas, Texas 75235

Phone: (214) 456-6220

General Inquiries: research@childrens.com

Intranet: https://dallaschildrens.sharepoint.com/Research%20Administration/Pages/default.aspx

External website: https://www.childrens.com/

Scottish Rite for Children

Scottish Rite for Children is an affiliate of UT Southwestern and specializes in the treatment of pediatric orthopedic conditions and sports injuries, as well as related neurodevelopmental and musculoskeletal conditions and certain learning disorders, such as dyslexia. The mission of Scottish Rite includes quality clinical care, innovative research and teaching programs.

Scottish Rite has two primary locations: Scottish Rite for Children Orthopedic Hospital in Dallas and Scottish Rite for Children Orthopedic and Sports Medicine Center in Frisco, as well as a satellite facility, Scottish Rite for Children at The Star in Frisco.

Scottish Rite for Children's long-standing history of treating orthopedic conditions began in 1921. Today, their physicians are considered leaders in the field of pediatric orthopedics. They all hold appointments at UT Southwestern Medical Center and are renowned for extraordinary patient care, outstanding research and teaching of medical students, residents and fellows from around the world.

Scottish Rite has six Centers for Excellence in: Spine, Limb Lengthening, Hand, Foot & Ankle, Hip, and Sports Medicine. Scottish Rite has state-of-the-art Movement Science Laboratories at both the Dallas and Frisco locations.

The Division of Clinical Research, Department of Research conducts Human Subjects Research at Scottish Rite for Children. Research studies include clinical drug trials, device trials, multi-site research, surveys, dyslexia education evaluations, intervention studies, observational studies and prospective/retrospective chart reviews.

As a UTSW Affiliate, Scottish Rite uses the UTSW IRB. Therefore, all Scottish Rite research staff must meet all UTSW credentialing standards and follow all policies and procedures. Scottish Rite does not provide training, credentialing or other services for staff not involved with research at our facility.

For all research using Scottish Rite as a performance site, there is an additional review process through the Scottish Rite Research Advisory Panel (RAP). Submissions are due by the last Friday

of each month. The RAP meets monthly to review all proposals.

More information is available here: https://scottishriteforchildren.org/research-and-education.

Main contacts in case of questions or assistance:

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Texas Health Resources

Texas Health Resources is a faith-based, nonprofit health system that cares for patients across North Texas. Texas Health Research departments are located within their Human Research Protection Program Office (HRPPO), Research Administration (RA) and Clinical Research Trials office.

All human-subject research conducted by THR employees/THR-credentialled individual or at a THR hospital/clinic or that is accessing THR data must be reviewed and approved by the THR HRPPO and THR Research Administration **in addition** to the IRB **prior** to beginning the research project. The Human Research Protection Program Office (HRPPO) is responsible for ensuring that all THR engaged human-subject research is conducted ethically and in compliance with federal regulations and THR policies. The Research Administration Office ensures all agreements and payments for procedures are appropriately in place, ensures appropriate patient billing and research coding are appropriately applied post study initiation, and reviews and sets up non-THR individual's access to THR systems or facilities.

All studies in which THR is a performance site must have a THR employee or THR credentialed individual listed on the study. The following items are required for all studies in which THR is a performance site:

- Completed Study Questionnaire
- Completed and signed Entity Reviewer form.
    - Both of these forms can be found under "Forms and Templates" at: https://www.texashealth.org/Research/Review-Board-and-Committee
- Other items may be required depending on the study specifics. Such items could include, but not limited to a Data Use Agreement, a THR Coverage Analysis, completion of Contractor Questionnaire and additional items related to being a contractor, Contractual agreement for services, etc.

After final review and approval, a letter from the THR HRPPO will be sent to the PI and study team noting site approval has been granted.

In addition to the above, the following are additional considerations when engaging in research activities at a THR facility.

Data

- **All data** that is being used outside of THR by non-THR individuals must at a minimum have a Data Use Agreement (DUA) in place. THR and UTSW have a Master DUA and for each individual study an Exhibit is created under that DUA.
- You may not send any THR data to another institution without prior permission from THR. This includes registries, other University collaboratives and/or other UTSW Affiliates (e.g., Parkland Hospital, Children's Hospital, etc.). THR requires a study specific Data Use Agreement with all other institutions receiving THR data even if that data has been combined with UTSW data.
- As part of the use of THR Data, THR must be noted in all publications stemming from the use of the data.
- THR has a Research Data Analytics team that can assist with research data requests. The THR individual listed on the study will be able to submit these requests or you can reach out to one of the THR Research Administration staff for assistance.

Access

- **Requesting access** to a THR system (i.e., electronic medical record) or THR hospital/clinic (e.g., to consent a patient, complete a survey, etc.) requires being credentialed by the THR hospital or be set up as a THR research contractor. This would need to be indicated while completing the THR Study Questionnaire and would be facilitated by RA.

Hospital Services

- If the study will involve **Hospital services**, a THR Coverage Analysis will need to be completed. Services will be reviewed as whether considered Standard of Care or not by Research Admin. Research Admin will provide any fiscal responsibilities to you for study related items.

For more information, go to the following dedicated website for THR Research: Research Administration (texashealth.org). Or, you can email the following:

THR Human Research Protection Program – HRPP@texashealth.org

THR Research Administration – THREResearchAdministration@texashealth.org

Chapter 3: Roles and Responsibilities of Research Team Members

A. Working as a Member of a Research Team

Effective Teamwork

The conduct and successful execution of a clinical research study is entirely dependent upon the team's efforts. 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 what is possible when all team members are fully engaged to accomplish the goals and objectives of the project. This is because solutions built on collaboration tend to be higher quality, longer lasting, and less prone to error.

Qualities of a Highly Functioning Team

- Interdependence. Interdependence is defined as the mutual reliance, or mutual dependence, between two or more people or groups.
- Trust. A relationship built on trust means a firm belief in the reliability, truth, ability, and/or strength of the other team members.
- Efficiency. Efficiency is the quality of accomplishing something with the least amount of wasted time and effort. The more competent the individual team members become in clinical research, the more efficient the team becomes as a whole
- Continuous and ongoing evaluation for further refinement. A highly functioning team learns from both its past mistakes as well as successes, discusses ways to improve processes, and then refines how they coordinate efforts so that each successive subject enrolled on a study has a more

Now that we know what the qualities of a highly functional team are, how do you create this team? Following are important information offered by researchers with subject matter expertise in this area:

Requirements for a Successful Team

- Knowledge of the resources required for project completion. Resources include the protocol, brochures, manuals, etc.
- Identifying the skills necessary for a successful project
- Involving all stakeholders. Stakeholders can exist not only within the team (e.g., the PI,

biostatistician, etc.), but also from without the team (e.g., department heads overseeing the work units where research activities will occur, etc.). The more each individual is notified about your team's planned study activities in advance, the more prepared you will be for any potential outcome

- Establishing effective communication procedures. 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.

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 and 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. Knowing that team members can rely on each other will make work less stressful.
- Facilitating relationships to initiate interaction
- Asking questions, listening, and taking advice
- Identifying skills and knowledge of each team member
- Clearly establishing the responsibilities of each team member

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, scientific 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 UT Southwestern?

Individuals with faculty or Clinical 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. If you are unclear on your PI status, please reach out to the HRPP at HRPP@UTSouthwestern.edu. You can also refer to the UT Southwestern Human Subjects Protocols policy for more information on this topic: https://www.utsouthwestern.edu/research/hrpp/assets/policy_5.1principal.pdf).

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 activities 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 subjects enrolled on the 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 an 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; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects.

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. PI's commit themselves to personally conduct or supervise the investigation. In the event of an FDA inspection, the Principal Investigator will be responsible for attesting that s/he supervised the conduct of the clinical investigation and protected the rights, safety, and welfare of participants in the drug or medical device clinical trial.

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; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects

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 depend 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 applicable) should be responsible for all research-related medical (or dental) decisions and care.

The FDA Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects) lists several, "instances in which study tasks have been delegated to individuals lacking appropriate qualifications."

The following are examples of tasks that the FDA have determined to have been **inappropriately** delegated during previous inspections at other research institutions:

- Screening evaluations, including obtaining medical histories and final determination if the subject meets inclusion/exclusion criteria
    - ***Rationale***: Since screening evaluations typically include assessing medical history, laboratory values, so forth, this activity requires a medical license to determine whether a study subject meets the enrollment criteria
- Physical examinations
    - ***Rationale***: This activity requires a medical license in order to perform all of the necessary components of a medical examination
- Evaluation of adverse events (AEs)
    - ***Rationale***: This activity requires a medical license in order to evaluate the qualities of the adverse event (e.g., seriousness, relatedness to the investigational product or treatment, so forth) as well as whether modifications in treatment that may be required to address the AE (e.g., discontinue treatment, lower the dose, so forth)
- Assessments of primary study endpoints
    - ***Rationale***: According to the National Center for Advancing Translational Sciences (NCATS), "An endpoint is a targeted outcome of a clinical trial that is statistically analyzed to help determine the efficacy and safety of the therapy being studied…

Endpoints may also be used to throughout a study to determine if a participant's risk of continuing to be in a study is too great." Based on this explanation, only medically licensed professionals can determine whether the study is meeting its stated primary study endpoints and/or whether a patient may need to be taken off study due to personal risks outweighing any benefit from continued study participation.

- Informed consent obtained by untrained and/or undelegated (i.e., not formally listed as study personnel with the appropriate regulatory body, such as the IRB) study staff
    - ***Rationale***: According to the FDA "A Guide to Informed Consent," the, "FDA does not require the investigator to personally conduct the consent interview. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research." In the end, the PI is responsible for oversight of all research activities under his or her protocol, including informed consent.
- Invasive sample or specimen collection (e.g., biopsy)
    - ***Rationale***: Invasive procedures are procedures in which the body is penetrated or entered (e.g., by a tube, needle, or ionizing radiation). Such medical procedures require a licensed professional to complete this task.

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 Investigator holds the IND/IDE 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-investigator assumes responsibility for tasks delegated by the PI. The sub-investigator 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-investigator, but not the Study Coordinator, also referred to a Clinical Research Coordinator (CRC). Nevertheless, it is generally accepted 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, great attention to detail and prioritize emergencies.*** 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 escalate any emergent issues to the PI in a timely manner (e.g., if there is a potential subject safety issue, the PI needs to be contacted so s/he can appropriately address).
- ***May be licensed or unlicensed personnel.*** Licensed personnel must work within their scope of practice. This includes licensed physicians, advanced practitioners (e.g., Advanced Practice Registered Nurses (APRegN), nurse practitioners, physician

assistants), 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

Under the FDA's guidance per 21 CFR 312.60, "An **investigator** is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation." Successful CRCs keep in mind that the **PI is ultimately responsible for the conduct of the study**. Thus, all study procedures must be carried out according to the PI's direction. Typical duties a CRC may perform *as directed by the PI* include, but are not limited to, the following:

- ***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 although this is a specific responsibility of the PI as outlined by the FDA, it is still a shared obligation by all members of the research team.
- ***Scheduling subject visits.*** When scheduling subject visits, the coordinator must often coordinate with many individuals, groups or other UTSW departments or clinics. This may include communicating with other members of the study team to ensure their availability for the conduct of study procedures, and most importantly, working with the study subject around his or her availability (to the extent allowed by the protocol). Depending on the subject population, individual subjects may need to coordinate study visits with his or her work schedules or to arrange childcare. While coordinating all these aspects may be challenging, 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 EPIC and documenting all communication with the study subject (e.g., phone calls

prior to the visit, email reminders, messages left via voicemail, etc.). There is also documentation that needs to be collected during the study visit. The documentation completed during a study visit could be as simple as documenting the time that all procedures (both standard of care as well as research-mandated) were performed. Or it could be more comprehensive, including documenting the subject's response to questions, updating their medical history or medications, and documenting any potential adverse events that will eventually need to be assessed by the investigator. Documentation also 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). Finally, the data may need to be transferred into an electronic data capture (EDC) 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 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 (e.g., such as by a phlebotomist).
- ***Abstracting study data from the medical record***. The coordinator may be asked by the investigator, study monitor, or other representative from a regulatory body to abstract data from the medical record of actively enrolled subjects in order to answer a specific research question or look for potential serious adverse events, such as from emergency department or urgent care visits. Or, if the study team is larger in size and can afford to allocate this responsibility to another team member, such as a Data Analyst, then the coordinator will need to work closely with this team member(s) to ensure that all information has been appropriately captured in a timely manner.
- ***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. After the PI has assessed the AE and any appropriate responses have occurred (e.g., adjusting treatment, titrating a dose down, etc.), the coordinator may report, or facilitate reporting of AEs or other Reportable Events (REs), 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 as in, updated in a timely manner. 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/CROrg 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.

Remember, at UT Southwestern, each employee must work within their scope of service/practice. It is important to be mindful that you must work in the scope you are hired into at UT, not the scope you may have credentials in.

For additional guidance on how to determine patient care task assignments, please refer to the Scope of Service for Healthcare Personnel in Clinical Research prepared by Ambulatory Clinical Education in the Office of Clinical Research. This scope of service document is located in the UT Southwestern Ambulatory Services Policy Manual, which you can access by going to the UT Southwestern Policies - MyUTSW website and going to the Policy Library search. Under, "Ambulatory Clinic Policy Search" you can review all of the policies, including AMB 5.02 Clinical Competencies and Scope of Service_Final.doc, which includes a link to the Scope of Service for Healthcare Personnel in Clinical Research grid. Please note: printed policies may have been updated – ALWAYS VIEW CURRENT VERSIONS ONLINE.

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 UT Southwestern, 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 are 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 (if they apply; UT Southwestern no longer date stamps informed consent forms with an expiration date) to

ensure uninterrupted project approvals

- Processing IRB approval letters and accompanying approved documents (e.g., 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/CROrg (as applicable)
- Preparing and submitting REs 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 may be required to perform or conduct.

Financial Staff

Financial staff play a key role throughout the life cycle of a 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 UTSWUT Southwestern 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 established grant/contract and/or 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 a recruitment plan to identify the target subject population, taking the protocol's eligibility criteria into account. The recruitment staff is integral to identifying recruitment barriers and implementing processes to overcome these 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.I), 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 CROrg to conduct some of the initiation and/or management activities that a sponsor is responsible for (e.g., monitoring).

UTSW Clinical Staff

UTSW clinical 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. UTSW clinical staff should always communicate with the study team if there are any subject safety concerns or if they are unsure if research procedures to be conducted. In the latter situation, since the Principal Investigator has already delegated all research-related procedures to the staff per the Delegation of Authority (DOA) log, then the research staff should be responsible for carrying out any research procedures, as necessary.

Nursing Staff

UTSW nursing staff caring for subjects participating in a clinical research study (for example, Advanced Practice Research Nurses, or APRsNs) should follow UTSW policies unless instructed otherwise in the research protocol approved by the IRB of record. 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 advanced information is an essential part of preventing protocol deviations.

Non-UTSW Registered Nurses Working at UTSW

Registered nurses who practice at UTSW, but who are not employed by UTSW (i.e., employed through a department), must obtain approval for practice at UTSW facility by Professional Staff Services and must be reapproved annually. Advanced practitioners, such as NPs and PAs who practice at UTSW, must be approved for practice by UTSW, as applicable.

There is no approval to practice as a Licensed Practical Nurse or Medical Assistant at a UTSW 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 and/or with the Office of Clinical Research.

For additional guidance on credentialing information and privileging processes, including Parkland Health and Hospital System as well as Children's Health, please go to the following website: Professional Staff Services (Formerly Credentialing) – MyUTSW (utsouthwestern.net).

Study Pharmacist

Though the PI is ultimately responsible for drug accountability, UTSW policies require the Investigational Drug Services (IDS), who employs a team of pharmacists and pharmacy technicians to perform the tasks of study drug storage, preparation, dispensation, and accountability (per UTSW policy RES-161). For more information about the IDS, refer to Chapter 11, General Support Services.

External Visitors

From time to time, external visitors may request to visit the campus's research and/or clinical laboratories. These visitors would be defined as any individual not employed by UT Southwestern or its affiliated hospitals (e.g., Parkland, Children's Health, and so forth). UT Southwestern does allow visitors to its research and clinical laboratories for educational or training purposes. Please refer to EHS-105 VISITORS IN RESEARCH AND CLINICAL LABORATORIES for more information on this policy and guidance on next steps that may be required to secure permissions.

Please note: This policy does not apply to the following: UT Southwestern students, employees, faculty, residents or fellows; visiting scientists and researchers covered by arrangements of the funders and home institutions; and guests who visit UT Southwestern for a short term and for a

specific event (i.e., serving as a guest lecturer, delegation member, site visitor or similar). For additional guidance, including observers in patient care areas, badge request form, so forth, please refer to Professional Staff Services and scroll to "Observers": Links – Credentialing (utsouthwestern.net).

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 for the study, so 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 member 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 the subject's participation in clinical research as positive an experience as possible.

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. This can be achieved by:
    - Treating participants, and their caregivers, with respect
    - Assuring a welcoming atmosphere where participants are seen
    - Identifying and resolving issues in a timely manner. If you experience any delays in resolving an issue, clearly communicate that to the subject and explain that you will follow up when you have more information and/or have reached a resolution. Transparency and constant communication is key in helping to defuse any issues as they arise
    - Additional considerations include:
        - Schedule appointments at locations that are convenient to the participant whenever possible. However, this is not always possible, especially when certain equipment (e.g., whole-body 3T and 7T scanners) are only located in a specialized facility, such as the Advanced Imaging Research Center (AIRC). In those situations, clearly explain the reason why appointments may need to occur at a specific location

        - Prepare for other necessary tasks, such as transportation reimbursement, gift cards with a flat compensation fee for participation, and so forth. Most likely, all of these situations will already have been negotiated by the financial team and ready for disbursement to the study subjects via an authorized payment system, such as ClinCards. If you have any questions about how to obtain ClinCards for the study, being trained on how to add funds, etc., reach out to the Sponsored Programs Administration (SPA)
- 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 about continuing their participation
    - Be persistent. Document all attempts to contact participants and keep trying.
    - Obtain prior IRB approval for all patient-facing documents that will be given to subjects at any time during the study. This includes:
        - 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 (e.g., special event cards, thank you notes)
        - All 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 consideration to maximize the potential benefits while minimizing any 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 accidental disclosure of sensitive findings (e.g., disease status, genetic results, etc.) that result from participation on 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 one of the five senses, 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."(eCFR :: 28 CFR Part 46 – Protection of Human Subjects)

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.

Effective October 1, 2017, Certificates of Confidentiality (CoCs) are automatically deemed to be issued for any NIH-funded research that collects or uses identifiable, sensitive information that was on-going on or after December 13, 2016. More information about these automatic NIH CoCs is located here: CoCs for NIH-funded Research | grants.nih.gov.

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, especially those related 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 also considered an integral member of the research team. Their role needs to be highlighted during the informed consent process and reinforced at each subsequent research visit. Responsibilities include:

- Adhering to the study visit schedule
- Complying with the study treatment
- Notifying the study team if there are changes in their current medications (including stopping a current one, adjustments in dosages, etc.) or new conditions/diagnoses made by their other clinical care providers during their study participation. For example, if a subject is on a cardiology study but during a standard clinic visit to their primary care provider is informed about an adjustment to their current medication as well as a new diagnosis, then this information needs to also be shared with the research team
- 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.

Many studies are starting to also request permission to contact the subject's primary care team, to relay any significant findings during subject's participation in the research study that could impact that patient's ongoing clinical care. If the protocol requires it, make sure that the primary

care team's contact information is current while the patient is on study.

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 of subtle, but significant, differences that need to be understood and carefully documented by the research team include but are not limited to:

- 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 to what the protocol may require
- 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

If you ever find yourself in a situation when you are unsure whether the information provided by the subject is important or not, or you are unclear what the scope of your responsibilities are, please reach out to your Principal Investigator or other resources (many listed throughout this handbook as departments, offices, and committees) for clarification and guidance. The wide-

ranging activities that occur throughout the life cycle of a study and that you capture as a part of the research team may end up having wider significance that could lead to a groundbreaking discovery or scientific advancement.

Chapter 4: Protocol Content Essentials

A. What is a Protocol?

The protocol is a study plan, or an investigational plan, which 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 their data can be combined 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 (IB).

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/

Finally, it should be mentioned that in the past few decades, the FDA has recognized a growing need to promote improved clinical trial design to reflect the changing demographic nature of the general population in the United States. Specifically, the FDA is interested in helping underrepresented communities become more involved in studies, and in November 2020 released

a guidance document entitled, Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. Per their document, "enrolling participants with a wide range of baseline characteristics may create a study population that more accurately reflects the patients likely to take the drug if it is approved and allow assessment of the impact of those characteristics on the safety and effectiveness of the study drug." Although this document does not establish legally enforceable responsibilities, it does provide helpful recommendations for investigators to consider when creating more inclusive studies that could potentially increase enrollment of underrepresented populations in their 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
- **Study Duration.** This includes 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**
- **Diagram.** A diagram or "schema" that represents the study design at a glance
- **Schedule**. The study schedule of assessments, also known as the protocol calendar or the schedule of events

E. Introduction/Background

The Introduction/Background section should identify the reason(s) for doing the study, any previous related studies and how they contributed to this study's design, and finally how this current study fits into the developmental plan for addressing a condition or disease. The introduction/background section is basically a brief discussion of why this protocol's novel inquiry is necessary. For instance, if there is an existing gap in the knowledge about a particular disease or condition, the introduction/background section will explain how it is anticipated that this new research protocol will address the gap. This section 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/Purpose

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

- State the primary objectives of the study (i.e., Purpose). For instance, you may want to determine the "efficacy" of Agent A.
  - Example: "To compare disease-free survival (DFS) as assessed by investigator for participants treated with Agent A plus pembrolizumab (i.e., standard of care) versus those receiving placebo plus pembrolizumab."
  - **NOTE**: One of the most important aspects of clinical research is that it can tell us how well a proposed intervention (i.e., whatever is being used to treat a disease or condition) works. Interventions typically include drugs but can also mean surgical procedures, lifestyle changes (e.g., exercise, diet programs), so forth. The *efficacy,* therefore, of an intervention is how well it works when compared to a placebo or no treatment at all. Efficacy can be measured in many different ways, such as how well the intervention improves symptoms, how long it takes for symptoms to improve with the intervention, or how many people respond to the intervention.
- State the primary endpoints of the study (i.e., how the objective is measured).
  - Examples of endpoints include, but are not limited to:
    - **Continuous measurements**: blood pressures, weight, blood chemistry variables. For example, Determine if Agent A lowers blood pressure by a certain number or degree
    - **Event times**: time to recurrence of cancer, survival time
    - **Counts**: frequency of occurrence of migraine headaches, number of uses of rescue meds for asthma
    - **Binary endpoints**: no recurrence/recurrence, major cardiac event yes or no
    - **Ordered categories**: absent, mild moderate, severe pain, New York Heart Association (NYHA) status
    - **Unordered categories**: categories of adverse experiences: Gastrointestinal (GI), cardiac, etc.
  - **NOTE**: An endpoint is a targeted outcome of a clinical trial that is statistically analyzed to help determine the efficacy and safety of the therapy being studied.

The sample size calculation is based on the primary endpoint.

- State the secondary, exploratory and or safety objectives and endpoints.
    - **Secondary** objectives are goals that provide further information on the use of the proposed intervention.
        - Example: “To compare overall survival (OS) for participants treated with Agent A plus pembrolizumab versus those receiving placebo plus pembrolizumab.”
    - **Exploratory** endpoints may include clinically important events that are expected to occur too infrequently to show a treatment effect or endpoints that for other reasons are thought to be less likely to show an effect but are included to explore potential new hypotheses.
        - Example: “To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of Agent A and pembrolizumab.”

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 so forth. This section should also include a schematic diagram of trial design, procedures, and stages
- A description of the measures taken to minimize/avoid bias, such as by employing randomization or blinding
- A description of the treatment(s) and the investigational product(s) being tested
- The expected duration of subject participation (e.g., in days, months, or years, etc.), and a description of the sequence and duration of all study periods, including any follow-up (as well as whether these visits will all be in person, over the phone, virtually, etc.)
- A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of the study, or the entire study
- Accountability procedures (e.g., study drug storage, handling, dispensing, and documentation of administration, return and/or destruction of the drug) 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 for emergency purposes

H. Selection, Exclusion, 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 are 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 mental 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 studies

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

Per the Office of Human Subjects Research (OHRP) and the Department of Health and Human Services (HHS), “Subjects have the right to withdraw from (i.e., discontinue participation in) research at any time (45 CFR 46.116(a)(8)). If a subject decides to withdraw from all components

of a research study, the investigator must discontinue all of the following research activities involving that subject's participation in that study (45 CFR 46.116(a)(8)):

- Interacting or intervening with the subject in order to obtain data about him or her for the research study (e.g., administering an experimental drug, performing a tissue biopsy, drawing blood, exposing the subject to visual stimuli on a computer monitor and measuring response times, orchestrating environmental events or social interactions, or conducting ethnographic interviews with the subject);
- Obtaining additional identifiable private information about the subject for the research study by collecting or receiving such information from any source (e.g., obtaining additional information from the subject's education records or medical records, or obtaining biological specimens pertaining to the subject that have been or will be obtained for clinical purposes and stored in a hospital's pathology department or clinical laboratory); and
- Obtaining additional identifiable private information about the subject for the research study by observing or recording private behavior without interacting or intervening with the subject (e.g., recording mother-infant interactions in the home environment using video cameras or monitoring messages posted on an internet forum that is password-protected and accessed by invitation only).

Sometimes, a subject wants to withdraw from the primary interventional component of a study, but is willing to allow the investigator to continue other research activities described in the IRB-approved protocol and informed consent document that involve participation of the subject, such as: (1) obtaining data about the subject through interaction with the subject (e.g., through follow-up interviews, physical exams, blood tests, or radiographic imaging); or (2) obtaining identifiable private information from the subject's medical, educational, or social services agency records or from the subject's healthcare providers, teachers, or social workers. When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue.

Continued participation in secondary components of a research study may be particularly important in clinical trials designed to evaluate the safety and effectiveness of specific interventions in the management of diseases or disorders. For this reason, OHRP recommends that when a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities

involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent may continue. OHRP also recommends that the investigator explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject."

For additional guidance and recommendations from the OHRP/HHS on how to withdraw subjects from non-exempt human subjects research conducted or supported by HHS, please refer to: https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/subjectwithdrawal.pdf.

I. Treatment/Intervention Plan

This section of the protocol 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 names
- Packaging (e.g., blister pack, bottles, etc.)
- 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 (i.e., a functional or anatomical change, resulting from the exposure of a living organism to a substance)
- Storage and stability
- Dose specifics
- Preparation (e.g., if the drug is delivered in a powder format and the investigational pharmacist needs to reconstitute it in normal saline first before it can be infused into a patient)
- Route of administration (e.g., intravenous, oral, patch, etc.)
- Incompatibilities (i.e., physical or chemical reactions that occur between two or more drugs when they are combined in the same syringe, tubing, or bottle)
- Availability
- Side effects (these include the ones that are known at the time of publication, but more may become possible while the research team is working with subjects. These are then reported to the sponsor, who will then update the appropriate essential documents, such as the Investigational Drug Brochure (IDB) as necessary to share this information with all of the research teams)
- Nursing implications (e.g., immediate emergency actions that a nurse must take if a certain side effect was observed during the drug's administration)

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. A washout period is when subjects receive no treatment or a different treatment than the one that is currently being tested in the study. The purpose of a washout period is to eliminate or reduce the effects of a previous treatment, which may affect the validity of the final results. For example, if you are doing a cardiology study and investigating a new drug for atrial fibrillation, then the patient may need to undergo a washout period for a previous drug (e.g., baby aspirin) to make sure that any effects, good or bad, observed with the investigational drug is due only to that drug, and not due to a combination of the drug with the baby aspirin. An important consideration to note is that any washouts of current drugs can only be decided by a licensed member of the team, who has been trained to safely make that determination whether a patient can be taken off of a current medication.

- Use of sham procedures (i.e., exposure to an inactive (or sham) procedure to assess the efficacy of an intervention, in this case against devices or procedures in a clinical trial)
- 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. Moreover, if a Legally Authorized Representative (LAR) or guardian is allowed to sign on behalf of the research subject (e.g., in situations where children are being recruited and too young to assent, or an adult may lack the capacity to comprehend, etc.), then this also needs to be clearly outlined, including the parameters where this instance would be allowed.

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
    - Example: “Disease-Free Survival (DFS) as assessed by investigator: time from randomization to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first.”
- *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
    - Example: “Overall Survival (OS) time from randomization to death due to any cause.”

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. As new information is discovered, this new data will then be disseminated to all of the centers participating in the research study, if it is a multi-center 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. It's important to note that the replacement of subjects is protocol specific and needs to be tailored to the trial's study design. For example, the following is a typical replacement procedure in a cancer study: a subject is withdrawn by the study team from the dose escalation cohort for any reason other than a dose limiting toxicity (DLT) prior to completing the first 28 days of [Agent X] treatment on a 28-day cycle. In this instance, since the patient never initiated the study treatment, a replacement subject would be enrolled and will be assigned to the same [Z] dose level so that the study still meets its objectives for enrolling [Y] number of subjects at [Z] dose.

Concomitant Medications

This section will address the use of other medications by subjects while enrolled in the study, including both over the counter (OTC) medications as well as prescribed medications. This section should describe the medications that are allowed (e.g., baby aspirin, statins) 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. Moreover, if there is a washout period allowed for the subject to stop taking a current medication before initiating treatment, then the duration of this washout should be thoroughly explained.

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 their first dose of study treatment (e.g., first pill, first infusion, etc.). Each study will clarify the specific criteria that define enrollment.

Study Procedures

The 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. If there is a study window of time allowed for completing each visit, this information should also be included (for example: Month 3 – Visit 3 (+/- 6 days). Also, if important details are necessary to clarify what is required and when, then insert that information as footnotes into the table. This will keep the table in a simpler format for ease of use, but also provide significant details that the study team may need when performing each study visit. An example of a footnote for the Physical Examination is included in the table below.

Table 2.

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[a]	X			X	
Venipuncture	X	X	X	X	X
Laboratory Tests [CBC, CMP]	X	X	X	X	X

Eligibility Review	X				
Drug Dispensation/Accountability		X	X	X	
Questionnaires/Surveys		X	X	X	

[a]Physical examination (PE): Complete PE at screening, including height (at Screening visit only) and weight; directed PE, thereafter, including weight.

Ultimately, the more information that is provided, the more likely that study teams will execute the protocol exactly as was originally intended. This will also reduce the number of errors and protocol deviations that could impact the scientific validity of the study.

O. Statistical Considerations

The study protocol should have a specified analysis plan appropriate for the objectives and design of the study. The Principal Investigator (PI) should clearly describe the types of analyses to be performed and evaluation techniques (endpoints, pharmacodynamic assessments, outcome measurements, etc.).

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. The following will be included in this section:

- 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 total 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 statistical 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 (i.e., fake/false) 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

In sum, the description of the analytical and statistical techniques utilized in the protocol should be as explicit as possible. All manipulations of the data should be explained, and the statistical methods to be used should be clearly identified. Simple statements about an "appropriate analytical technique" and an "appropriate statistical test" are discouraged; they imply that the investigator has not fully planned out the required analyses for the study.

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. 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 the quality management procedures include creating, implementing, maintaining and upholding/following standard operating procedures (SOPs). The Quality Management section of the protocol describes the procedures that will be used during the study to protect data quality and integrity. SOPs could be implemented at the department level, the program level, or for the specific study. A well-written SOP will support the following expectations and standards:

- 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 often requires that all clinical trials supported by NIH have a DSMP: https://osp.od.nih.gov/clinical-research/nih-data-and-safety-monitoring-policies/

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 actively monitored
    - Who will be monitoring and at what frequency (e.g., quarterly, annually)
- 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 (e.g., lab tests, physical exams, etc.)
    - How will the problems/side effects be handled by the study team
    - 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, etc.)
- 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: https://grants.nih.gov/grants/guide/notice-files/not98-084.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 I–Bs – Improving Human Subject Protection, January 2009: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adverse-event-reporting-irbs-improving-human-subject-protection
  - Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring

- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE (Bioavailability/Bioequivalence) 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 UT Southwestern Human Research Protection program policies related to recordkeeping and retention may vary in terms of the length and determining time point for records retention. If you are ever placed in a situation with conflicting retention timeline, always opt to follow the most conservative (i.e., longest term requirement) policy for your study.

U. Publication Policy

This section of the protocol should cover the publication policy, if not already addressed in a separate agreement. The research protocol should specify not only how the results will be disseminated in the scientific media, but also to the community and/or the participants, the policy makers, etc. Therefore, the publication policy goes further to lay down the groundwork for who will be acknowledged as contributors, who will be acknowledged, etc., in the event that the results of the protocol are published.

V. References/Bibliography

All study protocols, whether randomized-controlled double-blinded clinical studies or chart reviews, should contain a references/bibliography section. This is because this section will contain

a comprehensive review of the literature that supports the rationale for the current study and include previous investigations that lead the investigator to develop the specific research question for this new protocol. In addition, this section should include a justification of the research design and the use of any placebos.

Some points to remember:

- References should be used for any point that can be attributed to a specific source
- They should be sequentially numbered throughout the protocol

W. Supplements/Appendices

When additional information is necessary to support decisions made by the Principal Investigator, it should be included in an appendix. The Supplements/Appendices sections offers an opportunity by the study author(s) to provide researchers with any additional information that would be useful to successfully and accurately execute the protocol. Examples of content that can be typically found in this section include, but are not limited to:

- Study tables (e.g., height and weight to calculate a pediatric BMI)
- Supplemental material of documents such as flow diagrams or work-up tables. A properly constructed flow diagram can greatly clarify complex interactions
- Questionnaires
- A description of the analytical methodology
- Brief reprints from study journals

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 refer to research data**.** For the purposes of this handbook, **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 workflow 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 UT Southwestern 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, CROrgs, 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.

Regarding 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 primarily focus on the regulations relating to these records in more detail. Information in the Code of Federal Regulations can be found here: (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm).

It should be noted that The National Institutes of Health (NIH) recently issued a final NIH Policy for Data Management and Sharing (DMS Policy) to promote the management and sharing of scientific data generated from NIH-funded or conducted research. This policy, which became effective on January 25, 2023, "establishes the requirements of submission of Data Management and Sharing Plans (hereinafter Plans) and compliance with NIH Institute, Center, or Office (ICO)-approved Plans. It also emphasizes the importance of good data management practices and establishes the expectation for maximizing the appropriate sharing of scientific data generated from NIH-funded or conducted research, with justified limitations or exceptions. This Policy applies to research funded or conducted by NIH that results in the generation of scientific data." To review this policy, please visit: NOT-OD-21-013: Final NIH Policy for Data Management and Sharing.

Any NIH-funded study submitted after January 25, 2023, is impacted by this update. The new policy requires that PIs deposit their scientific data in publicly accessible data repositories at the time of, or before, the data is included in a peer-reviewed publication, or at the completion of a research project; and that a plan for how and where the data will be deposited is explicitly described in a Data Management and Sharing (DSM) Plan. The UTSW IRB does not need to approve the plan (that is the exclusive purview of the NIH to review the DMS Plan for adequacy). However, the IRB does need to see the plan and ensure that it's consistent with the study.

If you have any questions about these new NIH guidelines, please refer to the above-referenced policy or visit UTSW's intranet website, "**NIH Data Management and Sharing Policy**," which was created by the Office of Research Support and Regulatory Management (RSRM) to help guide researchers impacted by this update: NIH Data Management and Sharing Policy (swmed.edu).

The website includes a video presentation on the updates, templates available for download, etc.

Finally, in addition to the above NIH policy, the NIH has also released Supplemental Information to guide researchers, depending on the study's design. Please refer to the following as applicable to your study:

- Supplemental Information to the NIH Policy for Data Management and Sharing: Protecting Privacy When Sharing Human Research Participant Data: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-213.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Responsible Management and Sharing of American Indian/Alaska Native Participant Data: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-214.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Selecting a Repository for Data Resulting from NIH-Supported Research: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-016.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Allowable Costs for Data Management and Sharing: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-015.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Elements of an NIH Data Management and Sharing Plan: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-014.html

Please email datasharing@utsouthwestern.edu if you have any questions about this new policy or contact the RSRM Office at 214-648-0456.

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 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 a 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.

Throughout a study's lifespan, there will be many essential documents generated that need to be maintained by the research steam. These essential documents can be categorized according to the stage of the trial during which they will normally be generated:

1) before the clinical phase of the trial commences
2) during the clinical conduct of the trial, and
3) after completion or termination of the trial

A complete outline of the recommended essential documents can be found on the ICH GCP

Website (ichgcp.net).

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.

A quick note about the difference between monitoring and auditing:

- **Monitoring** is usually conducted by interested parties involved in the research (investigators, institutions, sponsors) to identify issues and to improve processes. The goal is quality control (QC) and quality improvement (QI), and it is usually conducted on a predetermined cycle, unless it is for cause (more on this topic is covered in Chapter 10). Frequent monitoring can identify data deficiencies that require a corrective and preventative action (CAPA) plan.
- **Auditing** is usually conducted by regulatory agencies (e.g., the Food and Drug Administration (FDA) or the Office for Human Research Protections (OHRP)) who operate under their regulatory authority to confirm that study requirements are being met. This type of monitoring is much less frequent and is based on regulatory requirements or concerns about the conduct of the study. Auditing can be random or for cause. Auditing can result in a corrective action plan, but it can also result in punitive action for the study, such as stopping all research activities or, in a worse-case scenario, debarment of the PI from participating in all current and future research activities.

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, CROrgs, 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 member 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 46.111*, *164.530(b)(1)*
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*, *5.11.1l, 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	• Investigational drug brochure • Package insert/prescribing	*ICH GCP E6 1.10, 1.48*, *2.4*, *4.6.3, 4.7*, *5.12.2,*

(As applicable)	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	*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, 5.11.1I, 8.2.2, 8.2.3, 8.2.7, 8.3.2, 8.3.3* *21 CFR 56.109* *45 CFR 46.109*
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, modifications, continuing review submissions, and study closure) • IRB correspondence (IRB notification	*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),*

	of reportable events, responses to reportable events. • Federalwide assurance letter • IRB roster or compliance statement	*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*
Monitoring/ Auditing	• Monitoring logs • Correspondence to/from study monitor • Monitoring reports (including site initiation and close-out) • Audit related correspondence (FDA,	*ICH GCP E6 5.18.4(g), 5.18.6*, *8.2.19-20, 8.3.10-11, 8.4.5* *21 CFR 812.140(a)(1)*, *812.140(b)(1)*

	sponsor, third party)	
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 considered "complete" when the data is deemed final (e.g., no additional data needed from the patient and/or access to the medical records, no more editing/analyzing of obtained data required, etc.). 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 UT Southwestern 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. UT Southwestern's policy on record retention is covered under FSS-201 RECORDS MANAGEMENT AND RETENTION. Per the policy, "**UT Southwestern records are state records** and it is UT Southwestern policy that these records, regardless of the medium in which they are maintained, must be retained for the minimum periods identified in the UT Southwestern Records Retention Schedule ("Schedule") as approved by the Texas State Library and Archives Commission ("Commission") and by the Texas State Auditor's Office , in compliance with Texas Government Code, Chapter 441. All Records Retention policies are supervised by Supply Chain Management: Records Retention - Materials Management (utsouthwestern.net).

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 many years to reach marketing approval. To address this, HRPP's policy on record retention states,

"The HRPPD retains all records (with or without participant enrollment) for six years after closure or cancellation, which is sufficient to meet federal, state, and local regulations, sponsor requirements, and organizational policies and procedures." 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 UT Southwestern Human Research Protection Program (HRPP) has developed a policy for recordkeeping (including access, storage and retention): https://www.utsouthwestern.edu/research/hrpp/assets/policy_8.3recordkeeping.pdf.

To review other UT Southwestern HRPP policies covering documentation, or to access additional policies and procedures that cover a wide range of topics, go to: HRPP Policies and Procedures: Human Research Protection Program (HRPP) - UT Southwestern, Dallas, TX.

Chapter 6: Study Initiation Process at UT Southwestern

Prior to initiating a study, the research team should be aware of the research setting in which they are conducting their research. In this context, “research setting” can refer to many different things, such as whether the study is engaged in some aspect of the larger community (e.g., school-aged children in Dallas Independent School District), involves recruiting patients within a private medical practice, requires permissions to access patient contact information from outside research networks, and so forth.

The process of initiating a study at UT Southwestern begins with the initial commitment to be involved in the study. This could take the form of a grant submission to the NIH or signing a confidentiality data agreement (CDA) with an industry pharmaceutical sponsor, etc. There are typically more activities that must be conducted if the study is investigator-initiated, as some of the necessary documentation required for IRB review are already provided by industry sponsors and/or the CROrg. The process below describes the most basic study initiation process for clinical research studies within UT Southwestern, but there may be additional requirements and steps in order to obtain final study approval, depending on whether there is involvement from any additional research settings. Moreover, these steps do not always occur sequentially; depending on the situation and/or sponsor, some activities may occur in parallel (e.g., a sponsor may work on the budget in parallel with regulatory review).

If you are ever unsure what to do at any point in the study initiation process, please reach out to any of the departments and offices referenced throughout this handbook for guidance.

Activity at UT Southwestern	Investigator-Initiated Process	Industry-Sponsored Process (NOTE: a Clinical Research Organization may be the point of contact)
Industry Sponsor makes initial contact with team to PI or other study team member regarding a new clinical trial	N/A	In most situations, the sponsor will make contact with the study team via email and include minimal information regarding their study (e.g., protocol title, a few eligibility criteria, etc.). Internally, the team will review this offer to gauge interest and feasibility. Usually, the Clinical Research Manager (CRM) will confirm that the patient population exists and start the process of determining who would be the PI for this potential new study. This could be achieved through a Disease Oriented Team (DOT), if it's a cancer study, or department meeting to discuss the proposal and secure consensus to proceed. The CRM should also ensure that the meeting minutes reflect the discussion and the preliminary plan for moving forward.
Feasibility Assessment Complete	Ensure the PI has the necessary resources and capabilities to carry out the proposed protocol (e.g., access to subject population, adequate time, and resources)	There is often a sponsor feasibility checklist that must be completed prior to the study team's feasibility assessment (sometimes referred to as a questionnaire). The CRM will complete this assessment with support from the Principal Investigator (PI). Other available resources are available on campus to complete this assessment (see Chapter 11). The most obvious question to be asked during a feasibility assessment is: can we recruit a sufficient number of patients for the study within a timeframe that is consistent with the projected funding? Once the feasibility is completed, one person should be responsible as the point of contact for any potential follow-up questions in order to prevent unnecessary delays.
Site Selection	N/A	The industry sponsor will determine whether the site meets the qualifications necessary to execute its protocol, based on the information that has been submitted through the feasibility. Occasionally, the sponsor may need to physically visit the site (known as a site selection visit (SSV), pre-site selection visit (PSSV), or site qualification visit (SQV)) in order to complete their assessment to review study spaces, laboratory facilities, equipment, etc. Expect to spend 2-4 hours of CRM time and approximately 30 minutes w/the PI. Consider discussing and providing a copy of startup fees so that the sponsor is aware of these when considering site selection. This may help avoid delay in approval of fees. NOTE: If Parkland is a site, confirm drug shipment is available for both sites. Once you are site selected, the study team will receive a formal notification from the sponsor or CROrg.

Ensure Confidentiality Disclosure Agreement (CDA) is in place in order to receive study initiation documentation	Ensure the grant/federal submission is complete and routed as appropriate.	Ensure the Confidentiality Disclosure Agreement (CDA) has been routed for signature as appropriate. The CDA may be required by the sponsor to release study documents to us. NOTE: the site cannot agree to the confidentiality statements often requested in the online feasibility questionnaires. The site **must** request a CDA. The department's manager should submit a request for CDAs through eAgreements. The process should not take longer than 1 week. Once the study team has a fully executed CDA in place, then the sponsor should send the following to the site since these items will eventually need to be submitted to the IRB for review. If any are missing, then contact the sponsor: - Protocol - Consent template - Investigational drug brochure (IDB) - Budget template - Contract template - Questionnaires (e.g., Quality-of-Life (QoL), Activities of Daily Living (ADL), etc.) - Central lab or Imagining manual (if available) - Pharmacy manual(s) (if available)
Protocol Development/Review / Consult with clinical research services that may be involved in the conduct of study procedures	The Principal Investigator is responsible for developing the protocol, although s/he may need to consult with other UT Southwestern research resources to assist with sections as needed (e.g., BERD to determine the appropriate power analysis and sample size calculation).	The sponsor will be responsible for developing and reviewing their protocol. They may receive assistance from the PI with drafting some or most of the contents. If so, their in-house scientific team will still sign off on all content before the study team receives the finalized version. Regardless of who has developed the protocol, the study team should still familiarize themselves with the study requirements and make sure that the team has all of the necessary equipment (e.g., 10-lead versus 12-lead EKG) in place. For instance, if any specialized equipment is needed to conduct the study, this is the time that the team should troubleshoot and prepare for all contingencies.

Become familiar with the investigational product	The PI will submit appropriate applications (IND, IDE) to the FDA, if necessary. Once this is done, review and become familiar with the investigational product (see industry-sponsored process for tips)	If appropriate, the PI should submit appropriate applications (IND, IDE) to the FDA. Meanwhile, review and become familiar with the investigational product. Although IDS will be responsible for storage, preparation, dispensation, etc., you still need to make sure all of the staff are familiar with the investigational product. For instance, does it need to quickly be administered to the patient, because it is only viable within 30 minutes after reconstitution? If so, then you need to make sure that you have the appropriate staff and resources to manage this (e.g., a dedicated staff member will need to be in contact with the IDS and get this to the RN ASAP). Or is the investigational product a pill, and has a diary that needs to be filled out by the patient? In that situation, make sure you are familiar with the log so that you can teach the patient how to complete it. Prepare all of your questions and reach out to the sponsor or CROrg as needed for clarification.
Develop an Instruction Manual or Manual of Procedures (MOP)	Develop (or review one provided from by a network) a manual to describe how to conduct all study procedures and complete the corresponding documentation.	Any study manuals are typically provided by the industry sponsor or CROrg. Familiarize yourself with the contents and plan a dry run through of all events that will need to be done during a typical study visit (e.g., if there are vital signs that need to be taken before, during, and after an infusion, make sure that the room has the appropriate equipment). Or if there are certain research labs that need to be drawn during the study visit, make sure you know where to bring the specimens for processing and work with the CLS to relay important information (e.g., a potential delay because the patient was late to clinic, etc.).
Budget Development and Negotiation	This likely will have already occurred during the grant submission process (which the PI handled prior to the start of this process). However, if you require additional guidance, reach out to Sponsored Programs Administration (SPA) to assist with all phases of this process.	The study sponsor or CROrg will send you a study budget that they created in house. This should be handed over to your financial staff team member and/or SPA representative. Our representative will then, in turn, review the budget proposal and begin budget negotiations with the sponsor. As needed, the research team may be consulted for assistance throughout this process (e.g., to confirm if all potential research charges have been captured in the budget. For this reason, it is important that the team has already reviewed the protocol and manuals to determine what additional research requirements, beyond standard of care, may be required to conduct the study. Any “research only” charges that have not been included in the sponsor’s budget should be referred to the sponsor to cover the cost). NOTE: coverage analysis will occur in tandem with the budget development and negotiations. The study team will initiate this process through VELOS, usually after the study has been submitted through

		eIRB. For details on this process, please reach out to SPA.
Create and/or review the Laboratory Manual	Create a laboratory manual, including processing instructions, related to specimen/sample handling.	The laboratory manual is typically provided by the industry sponsor or the CROrg. It will contain all of the information required to collect, process, store, ship, etc., all research-related specimens and samples needed for the study. This manual may include critical information that impacts on the budget, so make sure to review it thoroughly and relay any differences noted between what is standard of care and what the sponsor requires. Share this information with the staff responsible for the budget and contract negotiations.
Reach out to research resources that may be involved in the conduct of study procedures	Initiate communication with groups such as the CRU (if necessary), IDS, and so forth, that may be helpful for conducting your study. (Refer to chapters 2 and 11 for a list of available resources and contact information)	Initiate communication with groups such as the CRU (if necessary), IDS, and so forth to discuss the logistics of conducting the study and make sure that they are prepared to support the study team, as needed per protocol. Refer to chapters 2 and 11 to review the departments, offices, and teams at UT Southwestern that are prepared to support your team conduct the clinical research study. Outline what parties are responsible for managing what aspects of the protocol, and make sure everyone has the contact list for all other team members in case they need to be reached. If any potential problems are identified, work with these departments to create solutions and workarounds.
Route Contract/Agreement through eAgreements	Ensure the grant/federal funding related documentation is complete and routed as appropriate. Reach out to SPA for guidance.	Ensure the Clinical Trial Agreement (CTA), or contract, has routed for signature as appropriate. This would have been initiated through the eAgreements portal. By default, most users have standard access to eAgreements. For access to the website, go to eAgreements - IR Products and Services (utsouthwestern.net). SPA can provide support throughout this process.
Draft the Informed Consent Form	Refer to the UT Southwestern Human Research Protection Program (HRPP) website and use the applicable template(s): Human Research Protection Program	The industry sponsor or CROrg representative will usually provide the study team with their own informed consent document utilizing their own template. If they have not provided one yet, request one ASAP. Although it's not required at UT Southwestern, the best practice is to utilize the HRPP's informed consent document template, which contains all of the FDA-required elements of consent and incorporate the sponsor's language into our local template. This way, the informed consent document already

	(HRPP): UT Southwestern, Dallas, Texas	includes any required site-specific language. Then you can work with the industry or CROrg representative to include their suggested language into the template.
Develop study data collection forms (visit/procedure checklists, worksheets, source documents, CRFs, etc.) and/or study database	Develop the study data collection forms and/or database to collect the necessary data in a consistent and analyzable manner (e.g., CRFs, Excel, REDCap)	Any data collection forms are typically provided by the industry sponsor or CROrg, usually in an electronic format using one of the major CRF platforms (e.g., Medidata RAVE, Medrio, Oracle InForm). These platforms are the databases that will also store all of the information from the study site(s) for the sponsor to review. The sponsor or CROrg will work with the study team to determine who all needs access and then schedule the appropriate training, as needed. This training will be done independently by the study team members.
Prepare and/or review Recruitment Materials	Develop a recruitment plan that is appropriate for your subject population and prepare recruitment materials. If the assets contain the UT Southwestern brand and/or logo, these also must be reviewed by CMPA to ensure that they meet the branding requirements.	Develop a recruitment plan that is appropriate for your subject population. If necessary, reach out for assistance from one of the research resources listed in chapters 2 and 11. Prepare to submit any recruitment materials provided from the sponsor/CROrg to the IRB for review and approval. Any patient-facing documents utilized to recruit patients must be submitted to the IRB for review to make sure that they do not contain language that is coercive or unduly influences subjects to participate.
IRB Initial Application Submission	All studies initiate in VELOS. From VELOS the study will be pushed to eIRB in "Draft" format. Finish the Initial IRB application (typically eIRB) using the electronic IRB software system (eIRB). Studies that will be routed to a central IRB, i.e., CIRB, WIRB, must first be	Create the study in VELOS. Once completed, VELOS will push the study to eIRB in "Draft" format. Finish the Initial IRB application (eIRB) using the electronic IRB software system (eIRB). Studies that will be routed to a central IRB, i.e., CIRB, WIRB, must first be submitted using the UTSW process. The IRB will need to review the protocol, consent form, and recruitment materials, at minimum.

	submitted using the UTSW process.	
Scientific/ancillary committee review (if applicable)	If any scientific/ancillary committee review is required for the study (e.g., the study needs SHUR to review research-related radiation, PRMC to review cancer-related studies), then their review will occur in parallel to the regulatory review by the IRB. Respond to any queries/stipulations ASAP.	If any additional scientific/ancillary committees are required to review any element of the submission (e.g., SHUR to review research required radiation, PRMC to review cancer-related studies), then their review will occur in parallel to the IRB. Scientific ancillary reviews and their final approval are required prior to the study receiving final approval and Investigator Relations Team (IRT) activation. For instance, if the ancillary review has occurred, but the study still has not satisfactorily addressed all conditions/stipulations released by the scientific committee first, then the IRT ***will not*** activate the study. Do not delay; address all stipulations/conditions ASAP to prevent any unnecessary delays to activate the study.
Initiate the ClinicalTrials.gov registration / FDA application submission as applicable	All necessary information must be submitted by the Responsible Party, which may be the PI if the study is investigator initiated. Reach out to the RSO for guidance. Any delays may create fines and/or inability to publish the data.	Typically, the industry sponsor is the Responsible Party for an industry study. In rare cases, this may be the responsibility of the PI if s/he is the IND holder, for instance. For any questions regarding this process, reach out to the Regulatory Support Office (RSO) for guidance: Regulatory Support: Human Research Protection Program (HRP-) - UT Southwestern, Dallas, TX
Create the Regulatory Binder (e.g., essential documents such as the DOA/Signature log, Training log, etc.)	Develop the essential documents and create the Regulatory Files/Binder to organize the documentation currently available. Use Florence for newer studies.	Typically, the industry sponsor or CROrg will supply the study site with the essential documents needed to for the site's regulatory binder. However, if any are missing, first reach out to them for a template. If they do not have one available, then contact the Clinical Research Office for the most recent templates available. File this information in the study's regulatory binder (either hard copy or virtual, usually managed by the sponsor/CROrg). This information will need to be filled out and reviewed by the time that the study receives permission to start actively recruiting (usually during the Site

		Initiation Visit (SIV)), so make sure that the documents are in order.
IRB Approval	Include a copy of the IRB approval letter in your regulatory files (paper), or upload to the Florence system (if a newer study)	Once your study has received final IRB approval, send a PDF copy of the IRB approval letter to the industry sponsor or CROrg. These are generated by the system once all stipulations and findings from the IRB and any other scientific ancillary committees have been satisfactorily addressed (e.g., SHUR, PRMC). If there are any other approvals required, such as from budget, contracts, etc., these must be addressed before the study team can receive the final Activation notice by IRT. Please note: Approval is DIFFERENT from Activation. Approval indicates that all regulatory requirements have been met. Activation means that the study is ready to start enrolling subjects since the budget, contract, etc., have now also been finalized.
Two weeks prior to SIV	N/A	Two weeks in advance of the SIV provide coordinators with a protocol packet to include protocol, fast facts, CRFs, and any other documentation required. A copy of the IRB approved consent form may be included, but the current version should be downloaded in real time when the study team is ready to consent a patient. Also: • Ensure all study supplies were delivered (SCCC and PHHS) • Ensure receipt of study drug. - If study drug has not yet been shipped, obtain a projected date of arrival from the sponsor/CROrg. Work with the IDS regarding any potential delays - NOTE: the sponsor may hold the release of investigational drug until the first patient is consented; however, every effort should be made to ensure that the drug can be expedited at that time to ensure availability for subject treatment
Site Initiation Visit (SIV)	Conduct a team meeting to review the protocol and related procedural details. If not already done, make sure to document all training on the DoA log as well as separate training log, if	The SIV is typically conducted by the industry sponsor/CROrg once all approvals have been secured. If the sponsor/CRO wants to conduct the SIV before the study has all approvals (e.g., the study has IRB approval but has not received final activation) that is fine, but they need to understand that the team will not be able to enroll any subjects until activation is in place. At the SIV the sponsor/CROrg will also conduct any last-minute training, review the essential documents to ensure that they are in place, etc. This SIV may be done virtually or in person and last anywhere from 30 minutes to a few

	applicable.	hours. Work with the sponsor/CROrg to make sure that you have a clear agenda of the topics to be discussed as well as a list of all personnel that are required to attend.
Open study to accrual	Complete necessary steps to open the study to accrual. This may be completed using the current trial management software	Complete necessary steps to open the study to accrual. This may be done using the current clinical trial management software.
Subject Recruitment / Enrollment	After the study is Activated in eIRB, the study is ready to begin recruiting and enrolling subjects.	After the study is Activated in eIRB, the study is ready to begin recruiting and enrolling subjects. NOTE: recruiting subjects may entail reviewing subject medical records, to determine eligibility. You may not engage in this research activity until the study has been "Activated" in the system. TIP: The CRM should send an open to accrual notification to the DOT team once the study is open to enrollment. This notification should include STU#, Study title, PI, primary coordinator contact information, sites that are open (SCCC/PHHS/ Ft. Worth), and basic I/E criteria. Meanwhile, the CRM should also: prepare and document additional training of staff as needed. This may include other department staff, physicians, research staff, clinic staff, inpatient staff, etc.

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. Policies and procedures for informed consent specific to UT Southwestern Medical Center can be found on the HRPP's website: HRPP Policies and Procedures: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

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 reasonably 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 questions 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 are 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 decide 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 with the information she or he would need to make an informed decision.

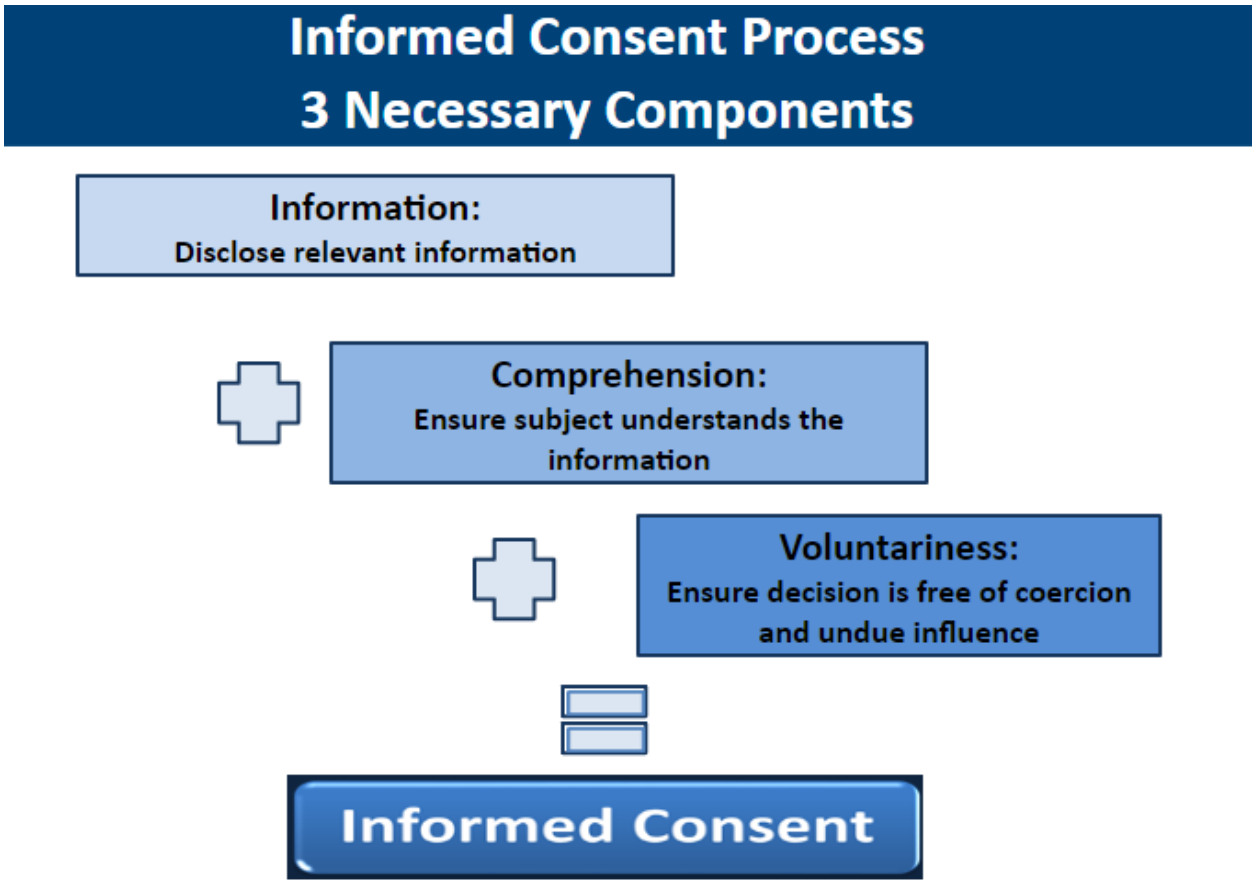
Comprehension

- 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.



A note about Undue Influence and Coercion

The Belmont Report states that undue influence occurs, "through the offer of inducements," which create, "excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (National Commission, 1978, p.8). It also argues that "unjustifiable pressures" occur when, "Persons in positions of authority … urge a course of action for a subject." This includes manipulating a prospective subject's choice by utilizing the "influence of a close relative." Undue influence needs to be distinguished from *coercion* for the purposes of UT Southwestern IRB applications of policy. **Coercion** is considered **the use of a threat of harm or punishment to influence behavior**. For example, a PI is using coercion if s/he informs a subject that they will lose access to needed health services if they do not participate in a research study. NOTE: in general, payments do not constitute coercion.

Other less apparent, but equally important, examples of vulnerability include **Institutional vulnerability** to undue influence and **Deferential vulnerability** to undue influence. Institutional vulnerability is when an individual is subject to the formal authority of others, which could unduly

influence the subject's willingness to participate. Examples of institutional vulnerability include prisoners, military personnel, students, and employees of the university. Deferential vulnerability is similar to institutional, but arises from informal relationships characterized by inequities in social status (e.g., gender, race, class), power (e.g., students taking a medical class as part of their curriculum, and then given a research survey by their instructor who is also the PI of the study), knowledge (e.g., doctor-patient relationship), or cognitive ability (e.g., elderly person defer to adult kids). In all these situations and beyond, the staff should maintain a heightened concern that subject's decision regarding participation in the study may not be truly voluntary. Deferential vulnerability can be very subtle, and as such investigators must be especially sensitive to the potential that subjects may believe that refusing to participate in a study will negatively impact their future treatment options (if a patient), class standing (if a student), performance evaluation (if an employee), etc. Investigators need to be sensitive to such deference and assess whether the subject is truly exercising his/her autonomy and adjust the informed consent process accordingly. In those situations, a suggested alteration to the usual consent process might include discussing study participation in the absence of the individual to whom the potential subject ordinarily defers. However, this may not always be feasible, since the PI or investigator with the existing working relationship with the patient may be the best person to discuss the study and answer questions; in those situations, it would not be appropriate to bypass them altogether.

For additional information about informed consent as well as other related topics, please refer to the HRPP Policy and Procedures guidance page: HRPP Policies and Procedures: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

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 about the study 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 in the training log as well as the DOA log.

Prior to approaching subjects to discuss their participation in a research study, please consider the following:

- Make certain to know the protocol and what is the purpose of approaching the subject to this specific study. Even if you are not able to thoroughly read the protocol from beginning to end, be familiar enough with the study parameters and the study schedule so that you can easily answer any questions.
    - Tip: the study schema and Schedule of Assessments/Events provide important information in an easy-to-understand format!
- Make certain to review the consent form before presenting it to a subject so that you present it to the subject in a way that conveys a clear understanding of the study. Tip: the consent form is another way to quickly grasp the most important elements of the study, including the purpose and requirements, before approaching the subject.
    - A quick comment: we recognize that although you may have been trained in the protocol in the past and this training was documented, some time may have elapsed since that initial training period. Some studies are so challenging to find patients that it may be months between study activation (and when the training initially occurred) and the first subject enrollment, for instance. In the meantime, you've been busy working on enrolling subjects to other studies, managing your portfolio of study assignments, and the important details about a protocol's specific study design may have been forgotten. *These tips are being offered to help you quickly get up to speed again.*
- Select an appropriate location to discuss the study. 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. On the other hand, a

crowded patient waiting room, busy cafeteria, or pre-operative area would be examples of locations that may *not* be conducive to conducting the informed consent process since your conversation with the subject could be heard by others.

- Ensure enough time has been set aside to review the study and the consent form in detail. Approaching prospective subjects on the same day that the research procedures would need to take place, if they agree to participate, may not provide sufficient time. Participants may need time to think about their decision or to discuss their potential involvement with family, friends, primary care physicians, social workers, clergy, a patient representative, or other trusted advisors. In the end, all discussions with prospective participants should take place with sufficient time for them to carefully consider his or her participation *without undue pressure*. It can be very difficult to absorb study details in one sitting, especially at a time of emotional distress (e.g., after receiving an initial cancer diagnosis). Whenever possible, 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 whether they want to participate in the future. For the best results, participants should be approached when they are willing to listen and are open and ready to consider the implications of this significant discussion.

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 before agreeing to consent. 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. NOTE: at UT Southwestern, the IRB has already incorporated all these required elements into the Informed Consent Form (ICF) template. Additional federal elements may be required, depending on the study's design. Moreover, UT Southwestern has adopted additional elements, all of which are incorporated into the informed

consent form template. The IRB can make the final determination whether any additional elements are necessary. If you believe that you need to delete any of these required sections from your study's ICF, please consult with the IRB first before attempting to make those changes.

Required elements of Informed Consent:

- 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 their time commitment.
    - Describe:
        - Number of visits (including whether any will be done at home, over the phone, etc.)
        - Tests that will be performed, including blood draws and laboratory tests (including any fasting blood draws). This area should thoroughly explain what is required and what may be optional
        - 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 (e.g., 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 and how it will be given (e.g., XXX provided to the child by a YYY gift card and XXX amount provided to the parents by a ZZZ gift card for each completed research visit). For additional guidance on HRPP's rules regarding compensation, please refer to Policy 4.1 Identification and Recruitment of Participants
- Identify any procedures that could be considered experimental
- Explain any reasonably foreseeable risks or discomforts to the subject. This includes:
    - Informing the subjects of the reasonably foreseeable harms, discomforts, inconveniences, and risks that are associated with the research activities in the study
    - Using understandable AE terminology or definitions for technical terms

        - Explain the implications of AEs that may not be familiar. For instance, if a study drug may produce a side effect that they have never heard of, explain what this AE will look like if it manifests, the importance of sharing all events with the study team, etc.
    - Conveying the likelihood of side effects. Terms such as “likely,” or “uncommon” are not helpful by themselves. Instead, use the consent form to help you explain the statistical probability of an event occurring. The UT Southwestern consent form template contains language that explains these probabilities in layman’s terms, such as, “in 1 out of 10 subjects…”
    - Describing 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 (also referred to as altruism), this should also 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 that are currently available to address the condition or disease
- Describe how the confidentiality of records identifying the subject will be maintained.
    - The OHRP Tips for Informed Consent further 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 need an NIH Certificate of Confidentiality (CoC) (https://grants.nih.gov/policy/humansubjects/coc.htm), which protects the investigator from involuntary release (i.e., under subpoena, which is a court order compelling someone to give testimony of the names or other identifying characteristics of research subjects). If the study has this in place, this should be shared with the subject so that they will be aware that their identifiable and sensitive information collected for the purposes of the study cannot be disclosed
- 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 UTSW HRPP policy regarding language guidelines to describe compensation and research-related injury language: Policy 3.1 Informed Consent Requirements.

- 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 UT Southwestern, these questions should be referred to UTSW Human Research Protection Program Office at 214-648-3060
- 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 HRPP website, UT Southwestern standard language is "You do not have to participate if you do not want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care. If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way."
  - If there are procedures that still must be conducted (e.g., for safety reasons) 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 is 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 *cannot afford them*)
- Describe how new information identified during the study, which 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 will 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 UT Southwestern HIPAA website: https://www.utsouthwestern.edu/about-us/administrative-offices/compliance/hipaa/.

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." Open-ended questions provide a platform for the subjects to respond spontaneously and encourages them to provide a detailed answer. Subjects should not be asked closed-ended questions that allow simple "Yes" or "No" answers since these tend to restrict the flow of the conversation.

The teach-back method is an effective tool to assess understanding. The person leading the consent process can ask the subject how they would explain the study to their relatives or friends. The interaction should be presented as an assessment of how well the person leading the consent discussion explained the study, not as a test for the subject. Areas that the subject did not understand are further addressed, such as with the use of open-ended questions, and discussed with the subject. A few potential open-ended 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?"

An open-ended questionnaire type assessment allows the researcher to get immediate and direct feedback about what the subject recalls from the consent process as well as what information may still need to be clarified. An informed consent assessment is not meant to be a pass/fail quiz, but rather 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. In those latter situations, reach out to your Principal Investigator for guidance.

To help subjects understand the information presented and so they have something to easily refer to later, they may be provided with additional IRB-approved patient-facing 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 the subject's questions have been answered and they have adequate information to make an informed decision to participate in the study:

- The subject and/or LAR (legally authorized representative or guardian; if applicable to the situation/study design), and researcher 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. Moreover, this is the standard adopted at UT Southwestern (See HRPP Policy 3.1 Informed Consent Requirements)
- 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. NOTE: At UT Southwestern all studies initiated after 2019 are utilizing a combined informed consent and HIPAA form
- NOTE: it is unacceptable to sign the ICF in advance of the consent process. The researcher obtaining consent may not sign prior to obtaining the subject's signatures.
- Be aware of the timing of events. When indicating the time that the ICF was signed, make sure that only AM or PM is clearly marked, not both or missing altogether. A considerable time lag between the time that the subject signs the consent and the researcher cosigns will raise questions. Do not back date or back time anything. If a true time lag occurred, clearly document in your research note *why* this delay occurred (more on Documentation of Informed Consents is reviewed later in this chapter)
- Follow the instructions as required for all sections of the ICF. If an area does not apply, mark it as N/A. Any blanks may appear that you forgot to review that section.
- If you make any errors while filling out the consent, strike through the mistake with one line and initial and date the error. If the subject made an error, instruct them on how to properly fix it. Do not assume that they understand that they need to initial and date their mistake.
- 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. If the subject is accidentally permitted to leave the premises without their copy, immediately contact them and notify them about this oversight, make arrangements to provide them a copy ASAP, such as mailing a copy to them (if they have already left and do not plan to return to campus within the next day or so). Record this conversation in the subject's research record, then arrange to send a copy of the consent form via certified US mail.

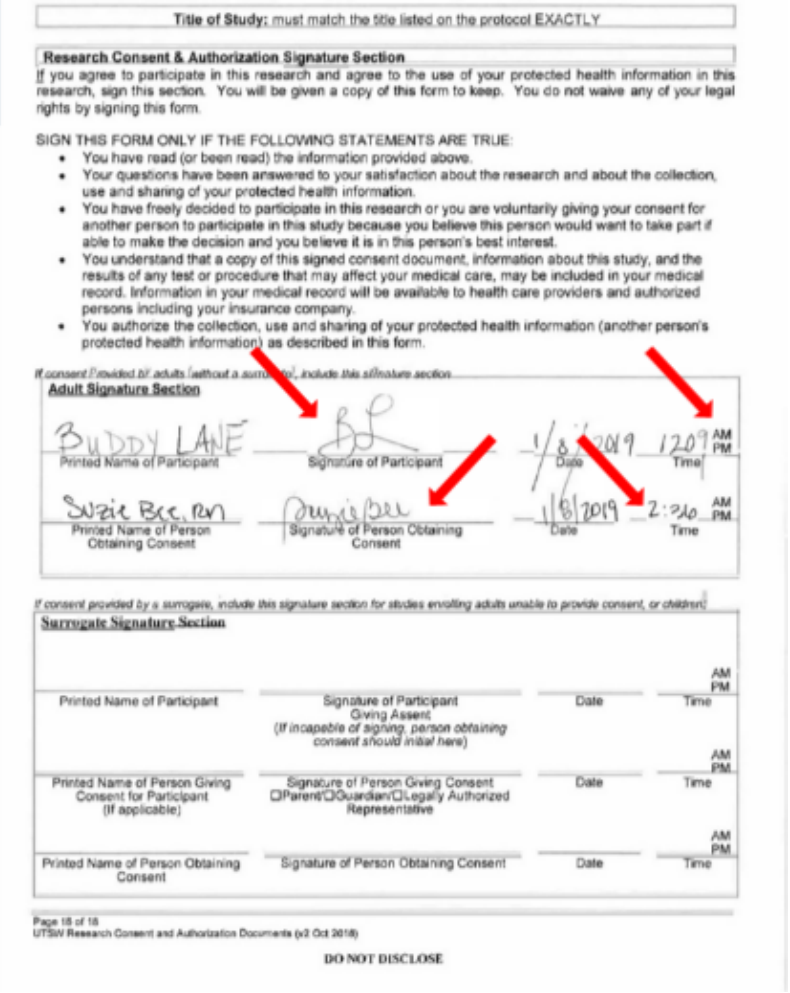
- The research team must verify that there have been no alterations to the consent form document itself before it is signed.

The following is an example of a consent form with several mistakes. For your convenience the issues that were noted have been marked in red. See if you can identify the issues without referencing the answers:

Improperly Completed Informed Consent

Errors:

- subject signed with initials
- AM vs PM not indicated
- initials for individual obtaining consent not included
- too much time between signatures of the subjects and individual obtaining consent



Title of Study: must match the title listed on the protocol EXACTLY

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research, sign this section. You will be given a copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE FOLLOWING STATEMENTS ARE TRUE:

- You have read (or been read) the information provided above.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.
- You have freely decided to participate in this research or you are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.
- You authorize the collection, use and sharing of your protected health information (another person's protected health information) as described in this form.

If consent Provided by adults (without a surrogate), include this signature section

Adult Signature Section

Printed Name of Participant	Signature of Participant	Date	Time
BUDDY LANE	BL	1/8/2019	1209 AM PM
Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time
Suzie Bee, RN	Suzie Bee	1/8/2019	2:30 AM PM

If consent provided by a surrogate, include this signature section for studies enrolling adults unable to provide consent, or children

Surrogate Signature Section

Printed Name of Participant	Signature of Participant Giving Assent (If incapable of signing, person obtaining consent should initial here)	Date	Time
			AM PM
Printed Name of Person Giving Consent for Participant (If applicable)	Signature of Person Giving Consent ☐Parent/☐Guardian/☐Legally Authorized Representative	Date	Time AM PM
Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time AM PM

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UTSW Research Consent and Authorization Documents (v3 Oct 2018)

DO NOT DISCLOSE

Legally Authorized Representative (LAR)

Obtaining legally effective informed consent of individuals before involving them in research is one

of the central protections provided in the regulations governing research. Informed consent in research is founded on the Belmont Principle's "respect for persons."

When the prospective research subject is a child or an adult whose own consent would not be legally effective because they lack the capacity to comprehend and give or communicate their informed consent, then research may be conducted only with the consent of the potential subject's parent, guardian or legally authorized representative (the "LAR"), which is also known as "surrogate consent."

For more information regarding HRPP's policy on LARs, including situations where the UTSW IRB may waive the requirement for obtaining surrogate consent (from a parent, legal guardian, or LAR), please review HRPP Policy 3.2 Informed Consent by Surrogate (Parents or Legally Authorized Representatives).

Use of a Short Form and Study Summary

The informed consent documentation requirements [21 CFR 50.27, 45 CFR 46.116, and 45 CFR 46.117] 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. The following are the signature requirements for the short form, per HRPP Policy 3.4 Informed Consent of Subjects with Limited English Proficiency:

1) Short Form (in participant's language):
    a) Signature of participant or legally authorized representative (required by OHRP/FDA)
    b) Signature of witness (required by OHRP/FDA)
2) English Informed Consent Document or summary:
    a) Signature of person obtaining consent (OHRP)
    b) Signature of witness (required by OHRP/FDA)

A copy of the summary is given to the subject or the representative (e.g., subject's LAR) 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 somewhere in a place that is

separate from the informed consent form. This documentation can 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 MyChart 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 demonstrate that study specific procedures are performed only after obtaining the subject's consent.

Remember: if it isn't documented, it did not happen! The consent form shows that consent was obtained, but documentation tells the story of the process.

Storage of the Signed Informed Consent/HIPAA Authorization Form Documents

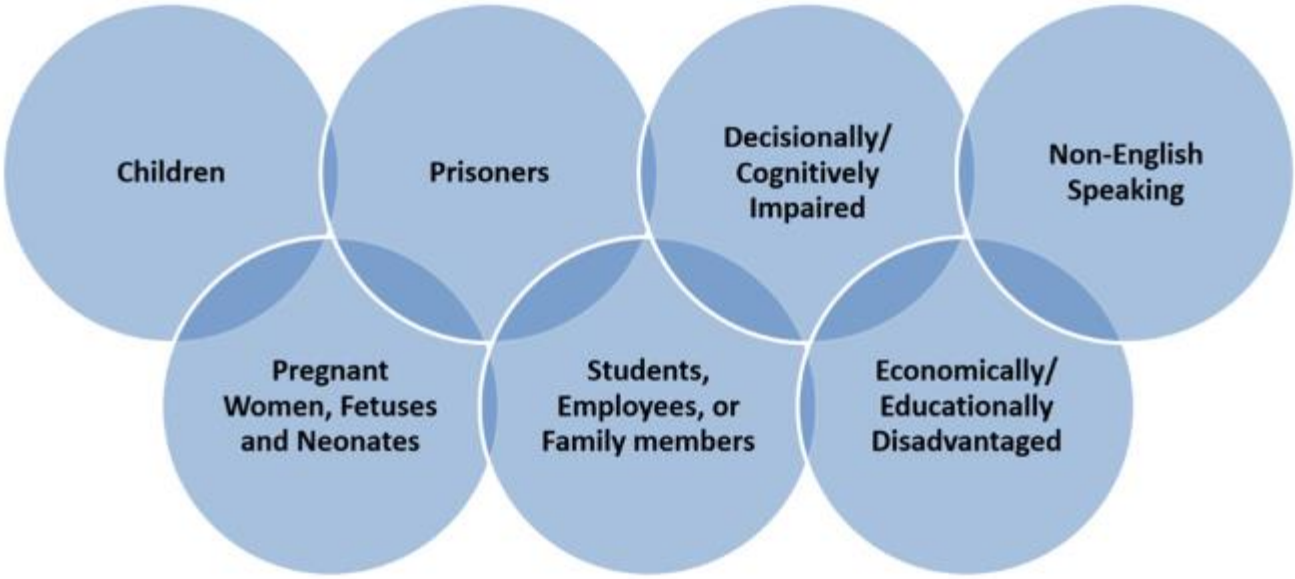
The original signed consent document must be retained in the study records. The original signed consent forms can be kept in the subject's research chart or in a binder intended solely for storage of original signed consent documents. If the university has adopted an alternate method of storing signed consent forms (e.g., uploading to a secure server), then work with your administrator to follow whatever are the current guidelines.

D. Ongoing Process

Obtaining informed consent is an ongoing process. Study staff should regularly consult with subjects throughout their participation in the study to ask if they have any questions, especially when they are required to perform or participate in new activities per the protocol, and if they wish to continue their participation on the study.

E. Challenges with the Informed Consent Process

The following sections will review situations and populations that may impact a person's ability to engaged in the informed consent process fully (i.e., without challenges), such as prisoners, persons with diminished autonomy (i.e., decisionally/cognitively impaired), etc. All the following are considered potentially vulnerable subjects in clinical research:



Federal regulations give special consideration to protecting rights and welfare of certain groups of vulnerable subjects. However, investigators must also consider other individuals or groups as vulnerable, such as those who are economically or educationally disadvantaged, minorities, the very sick, students, and so forth. Institutional policies are in place that outline the safeguards for these groups: HRPP Policies and Procedures: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

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 and/or their language of learning.

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 requires a translator to interpret for the person obtaining informed consent including translating any questions the subject may have and their answers. UT Southwestern's UHRI 05 Services to Persons with Limited English Proficiency or Sensory Impairment (Interpreter) – Hospital Policy, which applies to all individuals working in William P. Clements Jr. University Hospital and the Hospital-Based Clinics, states, "A qualified interpreter must be used *for all informed consents for treatment and procedures*." For various reasons, a subject may want to use a family member rather

than the hospital's qualified interpreter. However, concerns for using a family member for translation services include but are not limited to:

- Inadequate understanding of medical terms and research
- May not translate verbatim
- Not unbiased
- May not share all information (both directions)
- May be culturally/socially inappropriate

While a translator will assuredly assist 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 may use a short form consent document in the language preferred by the subject. The short form is only allowed for use with up to three subjects; after that, then a fully translated consent document must be used. 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.

Refer to the HRPP website for guidance on the consent process for Non-English or Limited English-speaking research participants:
HRPP Policy 3.4 Informed Consent of Subjects with Limited English Proficiency and
UTSW HRPP Guidance on Enrolling and Consenting Non-English Speaking Subjects

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. Texas law allows someone to sign by a mark, either an x or some other mark. The reason could be because of Illiteracy, personal choice, or disability.

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 the person (1) 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 but is not required.

The HRPP has prepared guidance within their Informed Consent Policy (HRPP Policy 3.1 Informed Consent Requirements) that specifically addresses how to consent illiterate subjects. Please refer to this policy for additional information or reach out to the HRPP at HRPP@UTSouthwestern.edu or by calling the office at 214-648-3060.

Subjects with Diminished Autonomy (Decisionally/Cognitively Impaired)

The first ethical principle in the Belmont Report, **Respect for Persons**, is made up of two important, yet distinct, requirements. The first is the recognition that people are *autonomous* and entitled to their own opinions and choices unless those opinions and choices are deemed harmful to others. The second is the recognition that due to various reasons, not all people are capable of self-determination and instead require protection for their own welfare.

Autonomy demands that the ability of competent subjects to make their own decisions be recognized and respected, while also protecting the autonomy of the vulnerable by preventing the imposition of unwanted decisions. However, an individual's autonomy can be affected by factors including age, cognitive impairment, illness, and treatments, among others.

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

An important distinction should be made about capacity. **Capacity** is a functional assessment and can vary over time (i.e., it is not static). Capacity to consent means a person has sufficient mental

capacity to understand the information provided, to appreciate how it is relevant to their circumstances, and to make an autonomous decision about participation in the study.

Determinations of capacity can only be performed by a licensed clinician who is familiar with the patient. If you have any questions about an individual's level of capacity, please reach out to your Principal Investigator or one of the clinical Co-Investigators on the study.

DHHS regulations require that a 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. For instance, some individuals may be only temporarily or intermittently incapacitated (e.g., due to acute 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 stop and obtain the participant's informed consent before continuing his or her participation in the study. If the investigator obtains informed consent from the subject, the original informed consent signed by the LAR should still be stored with the patient's research record and will be maintained as an important source document. However, the subjects' record will now also contain this second informed consent that has been signed by the subject.

Before proceeding to the next section, we should make clear that *outpatient* consenting for incapacitated adults looks different than what is described in the Priority for Consent Purposes (outlined in the next section). In outpatient situations, guardianship would be required for proper consent to occur.

For additional guidance from UT Southwestern's HRPP on consenting, including minors, please refer to the following group of policies: https://www.utsouthwestern.edu/research/hrpp/policies/#3. Children Participating in Research are covered in more detail later in this chapter.

Priority for Consent Purposes

The individuals below are in order of priority for consent purposes and are ONLY applicable to ***inpatient*** settings with patients who are ***adults***. Consult the individual in the order they appear only if the previous individuals are not available.

Subject with Capacity. If a potential subject has capacity to consent to the research, informed consent must be obtained from them. Capacity to consent is presumed to exist unless there is evidence to the contrary. If there is a question regarding a potential subject's capacity, a clinician will assess and evaluate the potential subject.

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. However, if the research needs to continue, a legally authorized representative (LAR) may be used to obtain consent.

Subject with a Guardian. A court-appointed guardian of the person, but not a guardian of the estate or guardian ad litem (i.e., an individual appointed by the court to represent the best interests in legal proceedings *only for the duration of the legal action*), may consent to a ward's research participation. Under Texas 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 Medical Power of Attorney. A Medical Power of Attorney for healthcare may consent to a potential subject's participation in research when they are incapacitated 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. Such determinations must be documented in writing. If there is any question from the research staff about the validity of a Medical Power of Attorney, please contact the Office of Legal Affairs: Legal Affairs: Administrative Offices – UT Southwestern, Dallas, TX

Subject with no Guardian, and no Medical Power of Attorney. If the potential subject is found to lack capacity and is in a home or community support services agency, or a hospital (i.e., inpatient) or nursing home or municipal jail, then the individuals listed below 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 and can consent in the following order:

(1) the patient's spouse

(2) an adult child of the patient who has the waiver and consent of all other qualified adult children of the patient to act as the sole decision-maker

(3) a majority of the patient's reasonably available adult children

(4) the patient's parents, or

(5) the individual clearly identified to act for the patient by the patient before the patient became incapacitated, the patient's nearest living relative, or a member of the clergy

The UT Southwestern IRB must approve the inclusion of subjects with diminished capacity to provide informed consent. This applies to adults as well as children. These populations cannot be enrolled unless the study clearly outlines the plan for identifying, recruiting, and consenting these groups and is expressly approved to do so.

The HRPP website contains guidelines when working with subjects with impaired decision- making capacity. Please refer to the following for additional information: HRPP Policy 2.6 Research Involving Individuals with Diminished Autonomous Decision-making Capacity.

Pregnant Women and Fetuses in Research

Additional considerations should be given when the study is enrolling pregnant women or women who become pregnant during their participation on 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 following definitions as defined by DHHS are important to review:

- *Dead fetus* means a fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.
- *Delivery* means complete separation of the fetus from the woman by expulsion or extraction or any other means.
- *Fetus* means the product of conception from implantation until delivery.
- *Neonate* means a newborn.
- *Nonviable neonate* means a neonate after delivery that, although living, is not viable.
- *Pregnancy* encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

- *Viable*, as it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration. The Secretary may from time to time, taking into account medical advances, publish in the FEDERAL REGISTER guidelines to assist in determining whether a neonate is viable for purposes of this subpart. If a neonate is viable then it may be included in research only to the extent permitted and in accordance with the requirements of subparts A and D of this part.

With the above in mind, the DHHS regulations require the following in research:

- Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, be completed prior to the involvement of pregnant women and provide data for assessing potential risks to pregnant women and fetuses
- 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

Pregnant women may only be involved in biomedical research if the study regards the health needs of the mother and the fetus will be placed at risk only to the minimal extent to meet the health needs of the mother, or risk to the fetus is minimal.

For these studies, the father's signature on the informed consent form is required unless:

- The study may provide direct benefit to the mother, or
- Risk to fetus is minimal, or
- The father is not reasonably available, or
- The pregnant was the result of sexual assault

Investigators, IRBs, and funding agencies must comply with requirements described in Subpart B of the DHHS regulations. For any questions about your study's inclusion of pregnant women and/or fetuses, consent requirements, etc., please reach out to the HRPP at HRPP@UTSouthwestern.edu.

Children Participating in Research

Children may not have the 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

A child is defined as a person less than 18 years of age unless legally emancipated. 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. Per DHHS, assent means, "a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent," whereas permission means, "the agreement of parent(s) or guardian to the participation of their child or ward in research." Subpart D — Additional Protections for Children Involved | HHS.gov.

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 considered 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. In general, in determining whether assent of children is required in all, some or none of the children in a study the IRB is guided by the following age ranges:

i. Ages 0-6 – The capability of children of this age group is so limited that they cannot reasonably be consulted. Assent is not required.

ii. Ages 7-10 – Children of this age group may be capable of providing assent depending on the maturity and psychological state of the children involved in the research. Verbal or written assent may be required but must not be waived by the IRB if the child is unable to provide assent.

iii. Ages 10 – 17 – Children of this age group are expected to be capable of providing assent. Written assent is usually required unless waived by the IRB.

The UT Southwestern IRBs have additional information regarding the assent/consent requirements for children participating in research. Refer to the HRPP Website for more guidance on the assent and consent requirements for children: https://www.utsouthwestern.edu/research/hrpp/policies/

Prisoners in Research

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. As defined by DHHS, prisoner, "means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing." Subpart C — Additional Protections Pertaining to Biomedical and B | HHS.gov. Please note that prisoners can include any person, adult or child, within the criminal or juvenile justice system.

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 by DHHS 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."

All the above is not mentioned to discourage the development of all potential research studies that target prisoner populations. In fact, the Secretary of Health and Human Services outlines research scenarios that could ultimately benefit this group, such as (i) the study of the possible causes, effects, and processes of incarceration, and of criminal behavior, (ii) the study of prisons as institutional structures or of prisoners as incarcerated persons, (iii) research on conditions

particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults), and (iv) research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In all these examples, DHHS encourages research with prisoners if, "the study presents no more than minimal risk and no more than inconvenience to the subjects."

All studies that include prisoners require full review by the IRB. IRB membership must include a prisoner representative, that is, someone who is knowledgeable of prison inmate life. If one is not on the board at the time of study submission, the IRB will locate one to assist with reviewing the study.

Students/Employees/Family Members

Students, employees, and family members are not considered "vulnerable populations" per federal regulations but are considered protected populations since they are susceptible to coercion due to their status as employees/students and/or family members of employees at the site. The IRB will have concerns whether these individuals' participation is truly voluntary for numerous reasons, including the individual's desire to appear cooperative or motivated.

To include this population in this study,

- These individuals must voluntarily agree to participate in the study
- Their employment status (if an employee) or family members' employment status must not be affected/impacted in any way
- Individuals may not be selected for research solely based on convenience
- Individuals must not work for the PI
- Privacy must be protected since these individuals are susceptible to peer pressure in the workplace

The following are some suggestions that the team can enact to reduce the possibility of undue influence on these individuals:

- Posting IRB-approved advertisements to recruit from a broad base of subjects. In this situation, the possibility of the recruiting a student, employee, or family member is left to chance
- Avoiding personal solicitations of by any person in an authoritative role (e.g., professor, manager, parent, etc.)

- If the person is a student, providing alternative and equal methods for meeting course requirements other than participating as a research subject

For additional guidance on this topic, including tips on how to modify your study so that you do not inadvertently create undue influence for any of these populations, please reach out to the HRPP at HRPP@UTSouthwestern.edu.

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 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. UT Southwestern's HRPP has addressed these situations by creating a policy (2.1 Initial Review of Research) that provides guidance on when the IRB can request assistance from a cultural consultant (e.g., cultural issues, the IRB does not have the appropriate expertise on the topic, etc.). Additional policies that address specific circumstances (e.g., cultural sensitivities during emergency research, addressed in 2.7 Guidance on Planned Emergency Research, Exception from Informed Consent, and Waiver of Applicability of Informed Consent), can be found in other sections of the HRPP Departmental Policy and Procedure Manual. Please go to this page on the HRPP website to access all the chapters.

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 UT Southwestern IRB website (HRPP 3.3 Informed Consent Waivers and Alterations) for more information regarding waiver of informed consent. Or, contact the HRPP at HRPP@UTSouthwestern.edu to request a consult with an Analyst to discuss whether your study may be eligible for a waiver or 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 subjects during the consent process.

UT Southwestern allows multiple consent forms within a study, but in all situations every consent must contain the required elements of informed consent per federal guidelines.

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. Or the person may believe that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge. These situations are called **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].

As a result of therapeutic misconception, 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

Any indication of therapeutic misconception during the informed consent process is detrimental to the subject's understanding of the study, which is crucial for a truly autonomous decision.

In order to minimize the possibility of therapeutic misconception, investigators should ***thoroughly*** discuss both the potential risks as well as the benefits of research as part of the informed consent process. Pay special attention to ensuring that any potential benefits of participating in the research study are properly characterized to the subject. Where the investigator is also treating physician, there exists a higher risk of therapeutic misconception. If possible, you may want to consider having an impartial third party obtain consent or finalize the consent process in the absence of the

individual to whom the potential subject ordinarily defers.

For more guidance on therapeutic misconception, please refer to the HRPP 10.0 Glossary of Human Research Terms and review the area under "**Undue Influence**."

G. Updates to the Consent Form/Re-Consenting

There are many reasons why a subject would need to be re-consented at any point during the study. For instance, if the original consent form or process was not properly executed, subject reaches age of majority, as required by the UTSW IRB or sponsoring agency, and so forth.

In addition to the above, 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 HRPP 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 (e.g., 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 life threatening, or severely debilitating side effects occur 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, 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 subjects before IRB approval can be obtained because of a potential immediate hazard, the researcher must report the dissemination of this information to the IRB within 5 business days. These situations are known as "Emergency Deviations," a type of Reportable Event, and are allowed if the event occurred to:

- Eliminate an apparent immediate hazard to subjects, or
- For IDE studies only: protect the life or physical well-being of a subject in an emergency

For more about the different types of Reportable Events and the different reporting timelines, please refer to Guidance & Resources: Human Research Protection Program (utsouthwestern.edu).

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

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 to the study. This includes whether another person was involved, such as a LAR. The goal is to make certain the subject and/or LAR understand the changes to make an informed decision as to whether to continue participation in the study. Moreover, the UTSW IRB must approve the revised consent. If the subject has reached "age of majority" (i.e., turned 18 while on study), then written consent should be obtained if the subject is still an active participant 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 considering the changes. The following should

be done during this re-consent period:

- The subject and/or LAR 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 and/or LAR should be provided the latitude to now decline any 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 significant new findings. The telephone call can be documented in the research record regarding when and who provided the new information to subjects and/or their LAR. 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 life threatening nor time sensitive.

Refer to the HRPP Guidance regarding Re-Consenting subjects for more information: https://www.utsouthwestern.edu/research/hrpp/assets/policy_3.1informed.pdf.

When Re-Consenting Subjects Should Not be Pursued

The IRB is aware that study sponsors often request or require researchers to present revised consent documents to the subjects to sign (i.e.-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 when they occur in the future. Consequently, the IRB generally disallows 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 IRB 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. Note: studies under the purview of UT Southwestern as the IRB of record no longer have an expiration date
- 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 (e.g., are past the relevant 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. As the subject's participation in the study continues, these communication styles should carry through until the end. When in doubt, always choose to be as transparent as possible about what will be done, when, and why. Every patient, whether enrolled on a study as a research subject or not, has a right to know about what will be done before it is performed. Encourage subjects to always contact staff if they have any questions or concerns.

Remember:

- 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 NEVER 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 should never be used to reject people for personal reasons. 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 (e.g., study participation may cause unacceptable risk to the subject) is excluded.

Study teams may pre-screen potential subjects with permission from the IRB (more on this in the next section). However, the subject's final eligibility is usually 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 all eligibility requirements stated in the protocol. Specific timelines for eligibility criteria must be reviewed. For example, a subject might need to demonstrate a "normal" ECG report within the last 3 months prior to consent. Or, the protocol might state that an eligibility waiver is allowed for an abnormal ECG, as long as it has been pre-approved by the medical monitor (listed on the protocol). In all situations, if you are unsure about whether a subject

has met the eligibility criteria for the protocol, reach out the Principal Investigator.

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 for the study. This signature and date attests 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 existing medical records when patients are scheduled for a clinic visit.

Potential subjects may be identified by clinical care providers or by the study staff using major eligibility criteria (e.g., 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 under the applicable "recruitment" activities.

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 (i.e., standard of care) if it is described as such in the protocol and the IRB application.

Identification and Recruitment of Study Participants

UT Southwestern patients may be contacted for potential participation in clinical research unless they have expressly indicated their desire not to be contacted for potential participation in clinical research; to "opt-out" of such contact. Patients cared for at UT Southwestern Hospitals and Clinics can state their preference not to be included in lists of potential research participants to be contacted, which was obtained by review of their electronic health record (opt-out). This does not prevent their treatment providers from informing them of research opportunities ongoing in their practice. Patients may change their preference to be included or excluded from potential research participant lists at any time.

The method used to contact patients for potential participation in research studies will be described

in the recruitment plan. Recruitment methods used to solicit volunteers into human research must be equitable and free of bias, undue influence and coercion. Recruitment methods must respect the privacy of potential research participants. The Institutional Review Board (IRB) must review and approve the methods, materials, procedures, and tools used to recruit potential research participants before they are implemented.

For additional guidance on best practices for identifying and recruiting patients, please refer to HRPP's policy 4.1 IDENTIFICATION AND RECRUITMENT OF PARTICIPANTS.

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 washout (i.e., the length of time that someone enrolled in a trial must not receive any treatment before receiving the trial's experimental therapy) or run-in period (period after inclusion, but before randomization to the study team; used to exclude potential ineligible patients) or receiving study treatment. At this point, the subject is most often considered enrolled and/or registered. At this point, the researcher should:

- Refer to the protocol for instructions on how to register/enroll study subjects
- Provide each subject with a unique sequence # or subject ID (usually assigned by the sponsor, or designed by the statistician, for instance)
- Make certain to keep copies of all registration documentation in the research chart

Please note that different trials will have different registration requirements, or some may have none at all (e.g., once the subject has signed the consent, this person may also be considered "registered" for all intents and purposes on that specific study). Do not assume that once the subject has consented to participate in the study that you have completed all of the initial work required for enrollment. Always refer to the protocol and/or Manual of Operations to define the specific registration procedures for the study. For any additional questions about study registration, reach out to the study sponsor and/or Principal Investigator.

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

Ensuring subject safety is a responsibility shared by all members of the study team, not just the Principal Investigator. The identification and effective management of all types of adverse events is integral to providing human subjects protection. Whether licensed as part of the clinical staff or operating as a clinical research coordinator, all team members are obligated to identify, track, and treat any issues as they arise to human subjects. The licensed clinical research staff have an ethical obligation to account for and treat adverse events associated with each subject's participation in a clinical research study. Meanwhile, the non-licensed research staff maintain timely oversight and thorough documentation of AEs as they occur during subject's participation in a study. All these activities are considered some 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.

An AE can therefore be any unfavorable sign, 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.***

Generally, AEs include:

- Clinically significant abnormal laboratory results (e.g., elevated liver enzymes)
- Development of NEW conditions during study participation, such as a new side effect or symptom (e.g., hair loss, tremors, etc.)
- Worsening of CURRENT conditions present at study enrollment (e.g., someone who had occasional headaches before starting treatment now experiences migraines, or more frequent headaches)
- Worsening of the CURRENT PRIMARY condition or diagnosis of the subject population (e.g., someone with elevated liver enzymes at the study outset progresses to cirrhosis)

It should be noted that when speaking to patients, a clinical research coordinator can only record

information about AEs (more about recording in section D of this chapter). It is the PI's and clinical co-investigators' responsibility to review the information and make clinical determinations about whether the study caused the AE (i.e., relatedness), if treatment is necessary, and so forth. Once you receive reports of any AEs under the criteria above, report them in a timely manner to a clinical member of the team.

Also, it should also be noted that there is an important distinction between the terms "Signs" and "Symptoms" in the medical field. A symptom is considered subjective evidence of the disease, which is what the subject will explain when he or she is seen in the clinic (e.g., "My head hurts more often now than it did before. The pain is sharp and lasts a few hours after my treatment). In this example, the research coordinator is unable to describe the pain; that is up to the subject on the study. On the other hand, a sign can be observed by anyone and is considered objective evidence of the disease. An example of a sign would be elevated blood pressure readings, abnormal CBC laboratory results, so forth. When recording information in the subject's research record, make sure that you are appropriately defining terms in your documentation.

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
- 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 after an investigational treatment was given (e.g., a protocol may state that any AEs that occur within 30 days after the last treatment dose are still considered SAE).

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. The following will be reviewed, but there may be other methods for gathering this important information, depending on the study's design:

- Open-ended questions
- Checklists of symptoms
- Standardized questionnaires

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?"

Please note that it can be difficult for all members of the study team to consistently ask the same question(s) and prompt the same responses when engaging with all the research subjects on a study. To illustrate, one experienced clinical research coordinator may ask all open-ended questions and gather more data, including AEs, from his or her subject, while a second, less-experienced clinical research coordinator seeing a different subject on the same day may only gather scant data, simply because he or she did not ask the same questions. To avoid these kinds of inconsistencies in study management, use checklists or standardized questionnaires whenever possible.

Checklists 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.

Some important considerations regarding checklists. First, checklists should be used with caution so that symptoms are not "suggested" to subjects. The study team may consider adding many potential symptoms, some of which may not be expected, so that the AEs reported are not biased only to those that are expected. Moreover, once a subject receives a checklist this is considered a source document and needs to be collected by the study team before that subject's participation ends in the study. Some subjects may forget to bring this checklist to their study visits, so the study team should build in time to call in reminders to the subjects prior to their upcoming study visit, to remind him or her to bring this important document. The study team members can also schedule periodic calls in between visits to remind patients about the checklist. Doing so will achieve two

things: make sure that important information is being captured in a timely manner, but also relay any significant information (e.g., potentially serious adverse events) to the study team so that the PI can determine whether the subject needs to come in and be evaluated sooner than what has been mandated by the protocol.

Standardized questionnaires:

The use of a standardized questionnaire helps ensure that all members of the study team inquire about AEs in a consistent fashion. Standardized questionnaires have been validated and demonstrated (1) to offer consistent responses across all subjects (i.e., reliability), (2) measure what they are intended to measure (i.e., validity), and (3) are able to differentiate between good and bad qualities (i.e., sensitivity). The questionnaire could include either open-ended questions or specific symptoms that are being solicited. If the study is sponsored, then the sponsor will provide all of the questionnaires needed to execute the protocol. If the study is investigator-initiated, the PI will likely either utilize questionnaires utilized as part of standard of care or obtain pre-existing validated questionnaires that have been successfully utilized for similar types of studies/populations.

In addition to the above, there are other types of study documents that could be used to help identify adverse events or prompt the study team to inquire further. These include:

Study documents completed by the subject

- TIP: 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. It is much easier to request clarification on an item that is unclear when the subject is still physically present, so that the source of confusion can be reviewed together.

Study documents completed by the research staff:

- *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. For instance, a patient may report that they are now taking Tylenol over the counter (OTC) for headaches. When you review the AE log for this subject, you do not see any mention of headaches in their medical history. A probing discussion may indicate that the headaches are (1) something that is seasonal, and they forgot to mention it, or (2) entirely new. In either situation, the appropriate documentation would need to be updated to present a

more accurate reflection of this patient's history.

- *Subject medical history* – inpatient and outpatient visit notes from the subject's medical record should be reviewed periodically to determine if any new problems have been 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 begin 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 subsequent study visits to determine if the symptom 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 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 (e.g., within 5 business days of the study team being alerted). 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**

  These must be documented. Whenever possible, keep a 12-month calendar handy so that you can refer to it during the study visit, if necessary.

- **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 these 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 National Cancer Institute (NCI) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm) 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 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 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, which states, "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 (Bioavailability/Bioequivalence) studies: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-reporting-requirements-inds-investigational-new-drug-applications-and-babe). 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. An unlicensed member of the team, such as a clinical research associate, cannot make these determinations since they have not had the appropriate medical training or experience.

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 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 likely 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 UTSW Simmons Comprehensive Cancer Center (SCCC) and the SCCC Data Safety Monitoring Committee (DSMC).

The following are guidelines to keep in mind when recording adverse events:

- **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 is 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://www.utsouthwestern.edu/research/hrpp/assets/re_tracking_log_upirso.docx

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 (RE) should **not** include PHI. UT Southwestern's RE reporting guidelines are available here: Reportable Events: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

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. An example of this is that headaches are expected as a side effect on a research study, but migraines (which are generally considered more debilitating than headaches) are not. Moreover, UPIRSOs are not limited to FDA regulated studies and can also occur in non-FDA studies. The FDA provides a helpful example list of unique types of situations in this document: (https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event)

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 IRB within 48 hours of learning of the event. If it is not immediately life-threatening, but meets the other criteria, it must still be reported to the IRB, but the timeframe for reporting will be five days.

The 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. https://www.utsouthwestern.edu/research/hrpp/assets/re_re_reporting_table.pdf

Safety Reporting to the FDA

It is important to know who is responsible for safety reporting to the FDA. Per 21 CFR 312.3l)(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 who holds an 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 (Bioavailability/Bioequivalence) 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 even– - If the event is **Serious**, **Suspected** and **Unexpected**
- The event must be reported no later than seven days (7) after learning of the even– - 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.

External UPIRSO's

An External UPIRSO is a report sent by a sponsor or IND holder that details an SAE occurring at another site involving the same study drug.

External UPIRSO's may be routed differently depending on how each department or research program is set up to handle them:

- PIs are expected to review all External UPIRSO's 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 External UPIRSO's to the IRB:

- If significant safety issues are identified that alter the risk: benefit ratio, the IRB should be promptly notified via a Reportable Event submission.
- If the event requires a revision to the informed consent form document in response to an External UPIRSO action letter, a modification must be submitted to the IRB promptly, along with the External UPIRSO.

Even if the External UPIRSO does not meet the criteria above, if the information is relevant to the study it may need to be submitted to the IRB using a Reportable Event (RE) Submission through the eIRB.

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 modification 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. Here are some examples:

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

Continuing noncompliance occurs after the initial report of noncompliance, and is defined by the UTSW HRPP as:

- A pattern of repeated noncompliance (in one or more protocols simultaneously or over time) which continues after initial discovery
- Includes inadequate efforts to take or implement corrective or preventive actions within a reasonable timeframe

For more information on HRPP's policy regarding noncompliance, please go to 9.3 Noncompliance Review, 9.5 Reportable Events Guidance, or refer to the HRPP website on Reportable Events: (https://www.utsouthwestern.edu/research/hrpp/reportable-events/).

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 contain 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://www.utsouthwestern.edu/research/hrpp/reportable-events/) 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 from 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 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 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 UT Southwestern's policy HSO-253 CLINICAL RESEARCH DOCUMENTATION IN THE

ELECTRONIC HEALTH RECORD for additional guidance on creating sufficient documentation in the electronic health record (EHR).

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 has 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 is 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 identifiable 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 IR Services 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 entitled, Electronic Source Data in Clinical Investigations, "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

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 serve 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 entitled, "Electronic Source Data in Clinical Investigations," "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. You can access the document here: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf) 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.

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 (e.g., 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 that 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, CROrg, 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 utilized since each event is unique.
- **Include the date the NTF was written, subject ID, and the study title, with IRB number**

and PI name.

- **Be legible.** The document should be legible if handwritten.
- **Explain the circumstances of the event**. Clearly explain the reason for the error, omission, or discrepancy and the process it aims to address.
- **CAPA.** Include any corrective and preventive action (CAPA) or follow-up, if applicable.
    - NOTE: The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. For more information on how to write an effective CAPA, refer to: Corrective and Preventive Actions (CAPA) | FDA
- **Signed.** Create a signature section at the bottom of the document. The document should be signed and dated by the individual who is writing it and the PI (if applicable).
- **Be filed with the subject document it refers to.**

A 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 (VELOS) 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 principal 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. Principal 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 UT Southwestern's Policy Handbook (**RES-161**) USE OF INVESTIGATIONAL PRODUCTS AND STUDY DRUGS IN CLINICAL RESEARCH, "It is UT Southwestern policy that all IP, study drugs, and placebo used for clinical research, including Food and Drug Administration (FDA)-approved medications and non-FDA approved investigational products, must be overseen by the UT Southwestern Medical Center Investigational Drug Services (IDS) Pharmacy, and must be handled consistently and in accordance with study protocols, as well as with all UT Southwestern policies regarding procurement, storage, inventory control, dispensation, and destruction of investigational products and study drugs."

Investigators conducting clinical drug studies must contact the IDS in advance for each clinical drug

research project to obtain an institutional feasibility assessment, Pharmacy/IDS budget estimate, and to determine drug handling requirements. Study drugs will be handled (defined as receipt, storage, preparation, dispensing, and destruction) by the pharmacy/IDS or IDS- approved delegate. At its discretion, IDS may delegate study drug handling activities to the investigator if both the study and investigator meet specific IDS 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 IDS involvement prior to subject enrollment and may be audited for compliance with study drug distribution procedures and institutional policy throughout the study. For additional information about IDS and its services in support of clinical research activities at UT Southwestern, please refer to *Chapter 11: General Support Services.*

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

- **DISPENSATION:** Dispensation is 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 (e.g., 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 IDS 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, if applicable, 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. The following are common terminology used in compliance monitoring.

Terminology

Data Integrity

Data integrity refers to maintaining and ensuring data is high quality (e.g., valid, accurate, and consistent). Data integrity covers the accuracy, completeness, and consistency of data over its entire lifecycle throughout a study. Data integrity is crucial for any organization as it ensures that the data that they rely on to make decisions is trustworthy and reliable. Human error can have a significant impact on data integrity. For example, data entry errors, such as mistyping a number or letter, can cause data to be inaccurate. FDA guidance documents refer to the acronym **ALCOA** when determining data integrity:

Attributable: It should be clear who has collected the data/performed the action and when it occurred

Legible: It should be readable with identifiable signatures

Contemporaneous: The information should indicate the accurate date/time the action was performed OR the data was collected

Original: The investigator should have the original source document

Accurate: Accurate, consistent, and free of errors

Compliance

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

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. Nevertheless, 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. The following are tips to verify consistency of CRFs with source documentation and to help stay "audit-ready":

- 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 any kind of diary, the study team should query any handwritten notes to determine if AEs occurred

Data Discrepancy

Data discrepancy is the 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 retrospectively date** the item. Put in the current date when the change occurs.
- **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.

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. At UT Southwestern, this means that for most PI-initiated studies where an IND/IDE is involved, the same monitor will return to the site. However, the PI (IND/IDE) holder does have the option to hire an outside source for monitoring. In those latter situations, it is up to the outside source to work with the PI for making arrangements to have the SMoR return for all reviews.

Routine Review (RR)

A routine review is usually a one-time QA review, although additional on-site reviews may be warranted due to findings discovered during the first visit. For instance, some initial visits lead to follow-up/additional visits (based on the number enrolled and how many subjects records need to be looked at), and sometimes a visit is scheduled to observe the consent process if subjects are still being enrolled. Protocols will be selected for routine review and prioritized based on, but not limited to, the level of risk. The level of risk in a risk assessment score can vary due to many factors including: the population included in the study, the situations encountered by the participants, and/ or the experience of the researcher or team, among others. In fact, two studies may appear similar, but a few factors could make one inherently riskier than the other. Moreover, protocols may be scheduled for repeated audits based on compliance results.

For Cause Monitoring

A “for cause” monitoring visit is a one-time review conducted at the request of an administrative official, entity, or agency, although more often than not these initial visits require additional follow-up visits. For-cause monitoring is conducted when concerns regarding research compliance, protocol adherence, or subject safety are brought to the attention of the reviewing IRB and may be initiated by the UT Southwestern IRB or other internal or external stakeholders.

What do auditors inspect?

- All IRB correspondence (submissions, email correspondence, etc.)
- Dated, IRB-approved consent forms
- Adherence to inclusion and exclusion criteria via individual subject’s 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

Ongoing Compliance Assessments Available Through UTSW

The following section will now delve into the specific departments that can assist the teams with

maintaining compliance at UTSW.

Quality Assurance and Monitoring (QAM)

The UTSW Quality Assurance and Monitoring (QAM) Office within the Human Research Protection Program (HRPP) focuses on serving the needs of UTSW research professionals by identifying areas of improvement and providing assistance to address them. The QAM office is vital in promoting and maintaining ethical research that is compliant with institutional policies, state and federal regulations, and best practices for protecting human subjects by reviewing and monitoring human research studies as well as conducting QA reviews of the activities of the IRB and HRPP Department.

The objectives of the QAM 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

Team Responsibilities for the QAM include:

1. Study Monitoring
    1. Research studies (routine and for-cause)
    2. Institutional Review Board (IRB) records
    3. HRPP activities and records
2. Provide routine monitoring for sponsor-investigator studies as required by FDA
3. FDA audit support

Investigators/Study Teams should contact the QAM Office when:

- They are notified of an external audit (FDA or any other external entity) by completing the Audit Notification to HRPP intake form via REDCap: Audit Notification to HRPP (swmed.edu) to request support for the audit ***and***
- To report allegations of noncompliance or subject complaints
- To request the services of the QAM program in fulfilling their responsibilities of monitoring as a Sponsor-Investigator holding the Investigational New Drug (IND)/Investigational

Device Exemption (IDE)

- To request a not-for-cause review and/or training upon study start-up or prior to study close-out. This can be done by emailing the QAM program manager

The QAM offers these additional helpful links to assist study teams stay in compliance with all regulations while conducting their studies:

- PI Self-Assessment Checklists: Reportable Events: Human Research Protection Program –HRPP) - UT Southwestern, Dallas, TX – SiteName

- UTSW HRPP Policies and Procedures: HRPP Complete P&P Manual (utsouthwestern.edu)

Finally, to obtain more information about the QAM Office and/or to request their services, please visit: Quality Assurance and Monitoring Office: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

Ongoing Compliance Assessments within the UTSW Simmons Comprehensive Cancer Center

The Data and Safety Monitoring Committee (DSMC) and support staff operate independently of the CROrg and PRMC. This committee is responsible for conducting risk-based monitoring for adverse events and protocol compliance and auditing for many UT Southwestern Harold C. Simmons Comprehensive Cancer Center (SCCC) trials based on a risk-level process. The committee accomplishes this through establishing a risk level for all newly activated cancer-related clinical trials; conducting annual comprehensive reviews for studies where the Simmons Cancer Center's DSMC is the DSMC of record, including evaluation of ongoing monitoring activities; conducting quarterly safety reviews; and conducting risk-based trial auditing. Some sponsored studies may also get listed for review by DSMC even if UTSW is not the DSMB of record, based on their risk level.

In addition, the DSMC staff conducts compliance reviews, known as Internal Audits (IAs).

Internal Audits

Internal audits (IAs) are conducted once per year on IITs conducted at the UTSW SCCC and its affiliates. This is usually done only for studies with a pre-determined risk level of moderate or high. Low-risk studies may be reviewed by the DSMC but are usually not audited. However, these low-risk studies may be audited if the DOT has not had any other study audited within the past year.

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 a response from the team is required, a Corrective and Preventive Action (CAPA) plan is put together by the PI to address any deficiencies that were cited in the audit. The DSMC reviews it at their next meeting and determines if it is acceptable.

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 may 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.

For any questions about quality assurance and monitoring through the SCCC, please go to Clinical Research Office: Simmons Comprehensive Cancer Center - UT Southwestern, Dallas, TX or call: 214-648-7097.

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 patient identifiers (usually a subject ID number), however additional information on the label may be site, department, or study specific. Be sure to check the MOP directions for proper specimen labeling since some identifiers may not be utilized by the PI.

- 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 handwritten, 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

Any person who offers for commercial transport (e.g., Fed-Ex, UPS, DHL, etc.) any biological materials (infectious or not) must meet the transport requirements set forth by the Code of Federal Regulations Chapter 49, and the International Air Transport Association (IATA). One of these requirements is proper training with regard to packaging and shipping biological specimens.

The US Department of Transportation (DoT) and the International Civil Aviation Organization (ICAO) regulate the shipment/transportation of items classified as Hazardous Materials (HM) or Dangerous Goods (DG). Any University faculty, staff, or students needing to ship hazardous

materials or dangerous goods must comply with the transportation standards established by The Office of Safety and Business Continuity (OSBC). The OSBC, working in coordination with the Chemical Safety Committee (CSC), the Institutional Biosafety Committee (IBC), and the Radiation Safety Advisory Committee (RSAC), is responsible for ensuring compliance with applicable laws, regulations, and best practices in the transport of hazardous materials. More information about this topic can be found in the UT Southwestern Policy Handbook: EHS-102 Intra-Campus Transport of Hazardous Materials..

By law, anyone who packs, ships, transports, or receives dangerous goods must be trained to perform these activities properly. The training is made available through the UT Southwestern's OSBC, and the Shipping of Biological Substances (IATA) training, both initial and refresher, are now offered online for UT Southwestern personnel who will be shipping biological materials. Please log into Taleo for access. If you have any questions, please contact Biosafety at biosafety@utsouthwestern.edu or call 214-645-1317.

The initial and refresher training courses require annual Bloodborne Pathogen Training before a certificate of completion can be issued. These courses in Taleo are three hours each and include the following:

- Pertinent regulatory definitions and shipping classifications covering dangerous goods (including infectious substances)
- The process to determine whether a biological material is exempt from regulation
- Proper procedures to package and label infectious substances for shipment by ground and by air
- The physical properties and hazards of dry ice
- The proper usage and packaging of dry ice
- Question and answer sessions
- Hands-on exercises
- Exam

IATA certification is valid for two years. The OSBC offers a refresher class for personnel who have previously attended the initial training class through our institution or have a valid certificate through Saf-T-Pak or DGI. Individuals who have received certification from other online companies or institutions must take our initial training class.

REMEMBER: if you need to ship bacterial samples, viruses, human or animal blood, serum, urine, tissue, cell lines, organs, etc., with or without dry ice, **this training is for you**. **DO NOT ship**

biological materials if you do not have a current certification.

Finally, it should be noted that 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)

Important: Failure to meet regulatory requirements when shipping hazardous material or dangerous goods may result in citations, fines, or imprisonment. Fines to the university can range from $250 to $500,000 per violation. Individual researchers and shippers may be subject to criminal penalties of up to $500,000 and five years' imprisonment. Do not take any unnecessary risks!

If you are unsure whether you are allowed to perform a specific task related to shipping items, or just require assistance with packing and shipping biological specimens, please reach out to the OSBC. Information specific to IATA Shipping of Dangerous Goods/Biological Substance Training is located here: IATA Shipping of Dangerous Goods / Biological Substance Training Schedule – Safety and Business Continuity (utsouthwestern.net).

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 the release of carbon dioxide gas while in transit. Dry ice must never be sealed in a container with an airtight seal. While in transit, as the dry ice evaporates, the courier will replace the lost weight with additional dry ice. Therefore, make sure that the amount of dry ice contained in the shipment is accurate.
- **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.

The following are not requirements, but suggested best practices for optimal specimen documentation:

- 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

There are various entities within the UT Southwestern clinical research environment that offer additional services to support ongoing efforts in research in the areas of technology support, general support, and governance resources. Many of these groups support services related to clinical care, but can also offer resources for conducting clinical research, such as the UTSW Clinical Research Unit (CRU). In addition, there are groups that only offer services for the purposes of conducting research, such as the UTSW Research Recruitment Participant Team located within the Clinical and Translational Award (CTSA) Program.

The specific services that you might require will vary on a protocol-by-protocol basis. For example, a protocol that includes the use of an investigational drug will utilize the services offered by Investigational Drug Services (IDS). There are many service groups described below. If you are unsure whether you require the services of a specific department, the contact information for each of the Services described below can be found within each section.

A. Technology Support Services

eIRB (electronic Institutional Review Board)

eIRB is a centrally hosted enterprise-wide web-based application used to manage lifecycle research, review and oversight processes for research. eIRB is UT Southwestern's Institutional Review Board (IRB) online submission system. It is designed for the submissions of human subject research protocols and related documents. Protocols submitted in eIRB are routed and reviewed electronically. Notification of study approval is sent via email to the staff designated in the system to receive these messages.

All studies that require regulatory review are submitted within the eIRB. However, if your project does not qualify for regulatory review (e.g., non-human subjects research), then that would be reviewed under a separate process. For any questions on whether your study requires regulatory review, please reach out to the HRPP via email at HRPP@UTSouthwestern.edu.

VELOS

VELOS is a study-management tool designed to help investigators manage the setup and day-to-day activities of complex human research studies. Access to Velos requires a valid ID and password for UT Southwestern, Parkland Hospital, or Children's Health (formerly Children's

Medical Center). NOTE: Academic Information Systems (AIS) will require 3 business days to process your request.

To gain access to either eIRB or VELOS, you will need to submit an eResearch Access Request Form from the eResearch website: eResearch Support: Academic Information Systems - UT Southwestern, Dallas, TX. Users requiring access must complete and submit the Request Access Authorization to a Research System form.

Details on training requirements for the Velos system can be found on the OCR website. Support, tip sheets and other Velos resources can be found here.

REDCap

As a member of the Clinical and Translational Science Awards (CTSA) community, UT Southwestern Medical Center offers REDCap – a self-managed, secure, web-based solution that is designed to support data collection strategies for research studies – to help researchers quickly develop databases for collecting and managing research data. To get access, go to AIS's website and submit a request form: Academic Information Systems: Information Resources - UT Southwestern, Dallas, TX. The REDCap support team is also available to answer any questions and can be reached via email: redcapsurveyadmin@utsouthwestern.edu.

Epic

Epic, or Epic Hyperspace, is the electronic health record system (EHR) used to manage UT Southwestern's patient services and data through a system of interconnected service modules. Epic is the software used at UT Southwestern and Parkland Health & Hospital System to house electronic medical records (EMR) - also known as electronic health records (EHR). You must complete Epic training before affiliated hospitals grant you full access to their EHR. More information about research EPIC training can be found on the OCR website. Further details and EPIC research tip sheets can be located here and on the EPIC website: EPIC (utsouthwestern.net).

Florence eRegulatory Management System

Florence is digital from start-up to close-out and allows teams to create, edit, distribute, collect, sign, and review all investigator site files, electronic logs, and participant binders electronically within a single platform. More information on the Florence Regulatory Management System is located under the Office of Clinical Research (OCR): Research Systems: Sponsored Programs - For Employees - UT Southwestern, Dallas, Texas

B. General Support Services

Ambulatory Clinical Education

The Ambulatory Clinical Education department, under the Office of Clinical Research (OCR), is tasked with assisting clinical researchers with learning the various technology systems that operate within UT Southwestern to facilitate clinical research. The Ambulatory Clinical Education department also offers classes (both virtual and in-person) to support researchers become adept at learning the various skillsets to successfully perform their job.

The following are educational areas covered within the Ambulatory Clinical Education department:

- **Scope of Service**. At UT Southwestern each employee must work within their scope of service. It is important to be mindful that you must work in the scope you are *hired* into at UT, not the scope you may have credentials in. You can review the document here: Scope of Service for Healthcare Personnel in Clinical Research.pdf (sharepoint.com).
- **Elsevier.** Elsevier is our online learning management system; this is where all of your online training will be stored. Credentialing will need copies of your transcript from Elsevier that you are able to save and print. Tip sheets are provided on how to access Elsevier, how to grade checklists if you are ever a preceptor, and how to print your transcript.
- **Taleo.** Our other online learning management system where you will enroll in your required classes both in-person or virtual, and this is where you will receive all your mandatory onboarding and yearly training from the institution.
- **Ambulatory Research Staff Skills.** This is a monthly course that includes online modules assigned in Elsevier for EKG (ECG) and Vital Sign training. There is an in-person didactic portion and skills check off that lasts about 2 hours total. You can enroll in Taleo by searching for "Ambulatory Research Staff Skills" and choose the date that works with your schedule.
- **Phlebotomy.** This is a monthly course including online modules assigned in Elsevier on phlebotomy techniques. There is an in-person didactic portion followed by skills training that lasts about 4 hours total. You can enroll in Taleo by searching for "Ambulatory Phlebotomy" and choose a date that works best with your schedule. You are not validated on phlebotomy after attending this course; you will need to have the name of your preceptor that can observe you performing the skill in a live environment at the start of the class, and they will receive instructions from me. You will also not be a licensed phlebotomist after attending this training. This course is for UTSW purposes ***only*** but may also be accepted at Parkland; please contact credentialing with any questions regarding Parkland's

requirements and how to successfully complete this requirement, if necessary. This class is extremely popular and fills up quickly, so sign up as soon as you know that you need this course for your role.

- **Heartsaver.** This class is offered throughout the month. The course includes both didactic and hands-only CPR training. You will receive a card that must be renewed bi-yearly. You can enroll in Taleo by searching "Heartsaver" (***one word***) and choose the date that works with your schedule. This course is required for your credentialing. Please keep in mind that this course is extremely popular and just because you receive a "nomination," it does not mean you have been accepted. You must wait for an "approval" notification before notifying credentialing that you are enrolled in the course.
- **SharePoint Site:** Ambulatory Clinical Education and Professional Development. Please utilize this site to learn any information about the Ambulatory Education Department. To the right of the page, you will be able to click "Clinical Educators" or "Meet the Experts" to find out more information about specific educators and/or request a consult with one of the staff.

Remember: if you are unsure whether your role requires specific training or classroom instructions, reach out to the Ambulatory Clinical Education Department! They are ready to answer your questions or provide clarification about classes, training, skills, or other learning opportunities. For further information about Ambulatory training requirements, please visit the OCR website.

The Aston Clinical Research Unit (CRU)

The Aston Clinical Research Core and Clinical Research Unit (CRU) is a fee for service institutional resource designed to support the conduct of clinical research. Located in the James W. Aston Ambulatory Care Center - UT Southwestern U7.601 & U9.300 and Zale Lipshy Pavilion - William P. Clements Jr. University, 5th floor. The CRU provides a set of standard clinical services to supplement resources provided through investigators' own departments and clinics. The unit is overseen by the Office of Clinical Research (OCR) and made possible and supported by UT Southwestern Medical Center.

The CRU offers the following services:

- Research Nursing services
- Research Coordinator services
- Facilities for outpatient and inpatient visits (with or without other services)
    - 23 Exam rooms
    - 6 Procedure rooms

  - 9 Consultant rooms
  - 2 Hospital rooms
  - Basic laboratory facilities and equipment
- Study drug infusions
- Point of care services
- Phlebotomy
- EKGs

Services are available to investigators who have UTSW IRB-approved protocols and signed Letters of Agreement with the Clinical Research Unit. For more information about the CRU please visit the website or send an inquiry to cruadministration@utsouthwestern.edu.

Research Participant Recruitment Team

The Research Participant Recruitment Team is supported both by the Office of Clinical Research (OCR) as well as the Clinical and Translational Science Award (CTSA) Program. The Research Participant Recruitment Team provides critical support to clinical research at UT Southwestern, as a successful recruitment strategy is one of the most important factors in the success of a study.

To overcome potential recruitment challenges, the Research Participant Recruitment Team offers the following services:

- **Feasibility analysis.** This is a review to determine how many patients we have at UTSW who meet the criteria of the study. This is usually initiated during protocol development, to determine if opening the study at our site is even feasible (i.e., capable of being done or carried out).
- **Recruitment planning.** This can occur at any time in study development and should happen before study initiation. A planning consult can help teams determine the location of potential participants (at UTSW, affiliates, or in the community), an outreach strategy, and budget.
- **Recruitment assistance if enrollment is slow.** This would occur after the study has opened and provides strategies to overcome enrollment barriers. The Recruitment Team can review the study and enrollment to date to determine if there are additional solutions available to increase participation.
- **1:1 or group training on query tools like SlicerDicer (Epic), i2b2, and TriNetX.** These tools can you help you determine how many patients potentially meet your study inclusion/exclusion criteria even before your study is IRB approved. Once you receive IRB

approval, you can then obtain identified patient lists.

- **Patient portal (MyChart) recruitment messages.** With IRB and OCR approval, study teams can approach UTSW patients through Epic's patient portal, MyChart. Patients receive an alert according to their preferences and can respond directly to the study team if they are interested in learning more. This is an easy and secure way to reach broad groups of UTSW patients.

If you have any questions about services, please schedule a consult with the Research Participant Recruitment Team here: Recruitment Team Consultations (office365.com).

Office of Community Health and Research Engagement

The Office of Community Health and Research Engagement (OCHRE) within the Clinical and Translational Science Award (CTSA) Program is committed to developing and sustaining community-academic partnerships that align community priorities and University research to improve health outcomes and equity, especially among traditionally underserved North Texas communities. OCHRE builds capacity for culturally sensitive, community-engaged research through the following resources:

HealthStreet community outreach program: Our community outreach team conducts health screenings (i.e., blood pressure, A1C, BMI) in community settings. We link those who screen positive to healthcare resources. Our presence in the community also allows individuals to become a part of our *Community Research Registry* if they choose. Through this registry, community members can get connected with research opportunities and our community outreach team can assist with targeted recruitment as needed and based on grant support.

Community Health Coalition: This coalition is comprised of multi-sector community leaders representing over 30 organizations. These organizations help advise on the most pressing community needs that we can help support as a research institution. This group also serves as a venue for collaborations to emerge both between these organizations and among organizations and researchers.

Community Engagement Directory: This online tool is a searchable database of community organizations, researchers, and community-engaged research projects, aimed to help facilitate community-academic partnerships. Researchers are welcome to submit a profile and to search the database for potential collaborators and to get a better sense of

the breadth of community-engaged research that exists at UT Southwestern as well as among our local academic affiliates.

Community Advisory Panel: Researchers may schedule a session with our panel of community experts. This is a group of diverse community stakeholders that advise on community needs and priorities and offer input on study design, recruitment, implementation, and interpretation of results from the client or patient perspective. This group is made up of Parkland patients as well as other community members who represent the demographic characteristics of the community. The panel can be tailored to the specific needs or target population of the study.

Spanish Language Resource: This service offers translation and cognitive response testing using an evidence-based process to ensure that English and Spanish study materials are accurate, culturally appropriate, and conceptually equivalent.

Education and Training: We offer a variety of education and training related to community-engaged research. Our CME-accredited *Community Engagement Grand Rounds* lecture series demonstrates best practices for the integration of community engagement activities into research to build sustained, community-academic partnerships. The full video library of lectures, along with links to obtain CME credit, can be found on our website.

For more information about OCHRE's services, or to schedule a consult, please go to: https://www.utsouthwestern.edu/about-us/administrative-offices/ochre/. Or you can contact the team via email at: OCHRE@UTSouthwestern.edu.

Biostatistics, Epidemiology, and Research Design

Housed within the Clinical and Translational Science Award (CTSA) Program, the Biostatistics, Epidemiology, and Research Design (BERD) Clinic's goal is to provide accessible consultative resources and innovative educational offerings to clinical researchers, and to develop new methodologies and tools, that advance clinical and translational science at UTSW.

The BERD clinic's expertise includes the following:

- Randomized trials and observational studies
- Power analysis and sample size calculation
- Missing data imputation

- Regression analysis (linear, logistic, Cox survival, Poisson regression models)
- Modeling of correlated data (clustered, longitudinal, multi-level cross-clustering)
- Causal inference
- Mediation analysis
- Meta analysis
- Difference-in-difference, interrupted time-series analyses

BERD's scope of support encompasses all phases of clinical research development and execution, from planning to final reporting. The following provides some examples of BERD's expertise within the following phases:

- Planning phase: experimental design, power analysis, analysis plan, protocol development
- Analytic phase: testable hypothesis, data elements (outcomes and covariates), modeling strategy
- Reporting phase: Tables and figures (pre-determined table shells and figure formats), interpretation, statistical method section, manuscript and revision

TIP to researchers: always seek Biostatistical support at the earliest stage! If you are unsure whether your study requires BERD clinic support, you can reach out to staff and attend one of their walk-in clinics or request a consultation with a BERD project manager. For guidance and additional resources, go to this website: Study Design and Statistical Support: CTSA – UT Southwestern, Dallas, Texas.

Research Design Studio

The Research Design Studio (RDS) is another office housed within the Clinical and Translational Science Award (CTSA) Program. The goal of RDS is to improve the facilitation of trial initiation and conduct in order to maximize the efficiency of both local as well as multi-center trials initiated at UT Southwestern. The RDS can assist with research study planning, implementation, design methods, contacting national collaborators, and overcoming local regulatory hurdles. The RDS helps investigators navigate CTSA/institutional resources and can help with the development of a study-specific stakeholder board.

RDS supports the following resources:

- Research Project Assistance, general help to start your clinical research project, and determination of applicable CTSA resources
- Research Protocol Design, strategic planning, and guidance for early-stage protocol

development.

- Multisite trial support, specific local resources, and services for investigators who are leading or participating in multisite clinical trials
- Partnership with National Trials, access to multisite networks such as TIN, PCORI & PCORnet
- Self-paced Educational Resources, information on project design and implementation, educational materials, and resources to assist with research protocol development.
- Partnership with Local Investigators, assistance finding local collaborators/mentors to support research studies
- Liaison to CTSA/Institutional Resources, resource navigation assistance for all aspects of research

The RDS also offers Q&A sessions and a 1:1 consultation to identify resource needs and to help address any potential roadblocks that may occur during clinical/translation research development. If a researcher is planning or taking part in a multisite/local research study and is unsure of where to begin developing his or her trial, please get in touch with the RDS to learn more about the services and resources they have available within the CTSA program: Clinical and Translational Science Award (CTSA) Program – UT Southwestern, Dallas, Texas.

Office of Clinical Laboratory Services Research

Clinical Laboratory Services Research (CLSR) is a fully accredited laboratory offering a broad range of testing from clinical laboratory and anatomical pathology services. Moreover, UT Southwestern's Office of Clinical Laboratory Services Research (CLSR) 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 excellent health care for the residents of the state of Texas

As a College of American Pathologists (CAP) accredited and Clinical Laboratory Improvement Amendments (CLIA) CLSR services support both sponsored and investigator - initiated studies. Before CLSR can process research samples for Lab Analysis, the following steps are needed:

- Approved IRB with STU #

- Coverage Analysis completed
- Performance Site Review Form completed
- Protocol finalized with clear instructions listing what specific labs are required
- Peer Review completed by both the A.P. and Core Labs
- Final budget uploaded after Peer Review is complete in VELOS
- "Active Enrolling" study status confirmed in VELOS

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, if necessary.

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.

More information about CLSR, including forms available for download for your study's sponsors (e.g., UT Southwestern's current CAP and CLIA certificates on file) is available here: Clinical Laboratory Services Research (CLSR) - Research Administration (utsouthwestern.net). Or you can send an email to the general inbox at: ResearchClincalLab@UTsouthwestern.edu and a member of the team will contact you.

Surgical Pathology

Specimens for testing removed by biopsy or through surgery are examined by an expert staff of faculty. In fact, the UT Southwestern Anatomic Pathology Laboratory provides internationally recognized expertise in Surgical Pathology, Cytopathology, Neuropathology, Hematopathology, and Pediatric Pathology. The Laboratory pathologists receive tissue specimens from the operating rooms and clinics. 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.

For additional guidance on Anatomic Pathology Laboratory services, including a listing of current subspecialty pathology services offered at UT Southwestern, go to: Anatomic Pathology Consultation Services: Pathology – UT Southwestern, Dallas, TX.

Investigational Drug Services (IDS)

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

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

UT Southwestern's IDS office provides comprehensive pharmacy services, which include:

- Protocol and study document review
- Budget proposals
- Participate in study meetings with Sponsor and with internal study team members
- Develop study specific procedures for the safe and efficient dispensing
- Facilitate of Epic drug files and treatment plans per investigational protocols
- Developed blinding procedures
- Provide drug storage and accountability
- Maintain Inventory management
- Preparation of study medications
- Record keeping and retention

Because IDS utilizes the standard medication distribution system of the UTSW, research protocols may run twenty-four hours per day, seven days per week.

More information about the IDS pharmacy is available at: Investigational Drug Service (IDS) - Office of Clinical Research (utsouthwestern.net). Policies that support IDS activities can be found on the **Office of Clinical Research (OCR)** website: Clinical Research - UT Southwestern, Dallas, Texas. The Investigational Drug Service Fee Schedule used for budgets can be found on the **Office of Clinical Trial Management (OCTM)** website: Office of Clinical Trial Management - OCRP (utsouthwestern.net).

C. Governance Resources

Research Compliance and Privacy

The Office of Research Compliance (https://www.utsouthwestern.net/intranet/research/ori/) coordinates and facilitates research policy, ethics, and compliance activities for research conducted across the UTSW 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 as well as within this handbook.

The Research Compliance Program collaborates with research offices and research teams to support various research activities and to ensure any associated risks are minimized for the organization. The program provides guidance to members of the research community at UT Southwestern in support of their conduct of multidisciplinary research and scientific training. Their efforts aid faculty, students, researchers, and study staff in:

- Recognizing compliance in their everyday practices.
- Anticipating and managing compliance issues that arise during projects.
- Preparing for new and changing requirements, regulations, and laws.

For questions regarding compliance and privacy issues at UT Southwestern, please go to the following website and contact the team: Research: Compliance - UT Southwestern, Dallas, TX.

HIPAA Privacy Office

The HIPAA Privacy Office ensures that UT Southwestern complies with the privacy laws, rules, and policies. Their office handles issues related to privacy practices, policies, concerns, and complaints. We also act as a resource for patients, staff, and students. The privacy laws provide for certain patient rights. These rights include:

- The right to receive a Notice of Privacy Practices (NPP)
- The right to confidential communications (to call you at a certain number or use a specific mailing address when communicating about your care)
- The right to request restrictions (access to your protected health information)
- The right to access your medical records or a record of releases of your health information
- The right to amend your medical records (to correct erroneous information)
- The right to an accounting of disclosures (to whom UT Southwestern provides information

about you)

To request a consultation with the staff regarding any of the above, and/or to access the additional notices on file with the HIPAA Privacy Office, go to the following website: HIPAA Privacy Office: Compliance – UT Southwestern, Dallas, TX.

Research Integrity and Responsible Conduct of Research

UT Southwestern Medical Center has a responsibility to guarantee that research is carried out both with the highest standards of scientific rigor and with the highest ethical standards. Research misconduct (also known as scientific misconduct) undermines the credibility of research within a research group and the whole institution, damages public trust in basic and biomedical research, and puts funding for current and future research projects in jeopardy.

Research Misconduct

Research misconduct is defined by both UT Southwestern and the federal government as *fabrication, falsification, or plagiarism in proposing, performing, recording, reporting, or reviewing research*. Research misconduct does not include disagreement in interpretation of data, nor does it include disagreements about authorship.

Instances and suspicions of research misconduct should be reported to the Research Integrity Officer (RIO). Initial reports can also be made to department or graduate program chairs, center directors, or deans, but all reports will be routed to the RIO. To contact the RIO, please go to the following link: Office of Research Integrity - UT Southwestern, Dallas, Texas. Reports may be made anonymously. Anyone who believes that they are experiencing retaliation for reporting research misconduct should contact the RIO and/or the Compliance Office immediately.

Information Security

Information Security works with departments across campus such as Information Resources (IR), Audit, Compliance, Privacy, Legal, University Police, and Safety and Business Continuity, to help safeguard UT Southwestern's goals and objectives.

The *Information* Security Department oversees the security of UT Southwestern's technology systems to ensure a safe and resilient computing environment that fulfills the mission of excellence in health care, education, and cutting-edge research.

The major technology areas that Information Security oversees and manages include:

- Security Consulting
- Technology and Data Risk Management
- Cybersecurity Operations
- IT Disaster Recovery
- Awareness and Training
- Security Policy and Standards
- Secure Email Portal

For more information about Information Security's services and support, please go to: Information Security – UT Southwestern, Dallas, TX.

To log an incident with Information Resources (IR), please submit a UTSW ServiceNow ticket: Log in | Authentication Required | SM (service-now.com).

NOTICE: All faculty, staff, and students are expected to immediately report any suspected technology security incidents or breaches to the Chief Information Security Officer or Information Security Department. To report a breach, please contact the IR Service Desk at 214-648-7600 or email IS at: infosec@utsouthwestern.edu.

Legal Affairs

The Office of Legal Affairs provides guidance to UT Southwestern Medical Center executive leaders, faculty, and staff to help advance our institutional missions in compliance with appropriate laws and regulations. The Office of Legal Affairs is a team of experienced attorneys, nurse risk managers, paralegals, and support staff that adheres to the highest ethical standards, and ensures UT Southwestern delivers care, research, and education the public can trust. The team has legal expertise in areas that impact a state agency and academic medical center, including constitutional, education, administrative, business, and healthcare law.

For additional guidance and to request their services, please go to: Legal Affairs (utsouthwestern.net). NOTE: Attorneys in the Office of Legal Affairs represent the University and cannot provide personal legal advice to employees, faculty, trainees, or students. None of the information contained on their website is intended to or should be construed as legal advice.

Biorepository Oversight Committee

The Biorepository Oversight Committee (BOC) is an Institutional Standing Committee under the President's Office. Institutional Standing Committees are established at the discretion of the

President to engage the expertise, perspectives, and institutional commitment of a broad cross-section of UT Southwestern faculty and staff on issues and activities related to the institution's mission, policies, and operations. Committee chairs and members are appointed by the President and serve in an important, advisory capacity, typically for one-year renewable terms. The Biorepository Oversight Committee ensures that biospecimens used for research are responsibly obtained, stored, and distributed and that the rights of individuals who have donated human biospecimens receive all necessary protections. More information about the BOC can be located in RES-155 Biorepository Oversight Committee – Handbook Policy (compliance360.com).

The University of Texas Southwestern Medical Center Policies

UT Southwestern Medical Center's institutional handbook policies are scheduled for review every five years. As each policy undergoes its scheduled review, the Policy Office adds notes about the changes to the Policy History section of the document. **Documents within the Policy Library represent the single source of truth for UT Southwestern institutional policies.** To access the policy library, go to this website: Policy Library - UT Southwestern Policies - myUTSW. You may be required to enter your institutional login credentials to access the library.

Clinical Data Sharing Committee

The Clinical Data Sharing Committee facilitates the disclosure of human-derived data with outside entities (typically commercial) for the purposes of advancing medical discoveries and extending the benefits of these discoveries to both patients and society in consonance with the mission of UT Southwestern. Not all disclosures require oversight of this committee. If the committee's review is required, you will be contacted. To achieve this objective, the committee aims to ensure that the data disclosure:

- adheres to sound ethical and scientific principles
- protects the well-being, safety, and privacy of those who entrust UT Southwestern with their care
- is transparent and preserves the trust that patients and the public in general place on UT Southwestern
- is prompt and secure
- makes best use of the resources entrusted to UT Southwestern
- complies with regulations and laws

For more information on Institutional Standing Committees, refer to the UT Southwestern Policy Library or contact the President's Office at 214-648-2508. Additional information regarding the many different institutional standing committees at UT Southwestern are located here: Institutional

Standing Committees - President's Office (utsouthwestern.net).

D. Frequently Asked Questions (FAQs)

This section contains additional information offered by some of the participating offices that contributed to the content of this handbook. They have offered bonus tips to assist you with questions they frequently encounter from researchers engaged at UT Southwestern.

The following offices contributed FAQs. Click on the link to go directly to their FAQ section:

- Institutional Biosafety Committee (IBC)
- Office of Clinical Trial Management – Performance Site Review (PSR) Form
- Protocol Review and Monitoring System (PRMS)
- Regulatory Support Office (RSO)
- Research Staff Credentialing Office
- Radioactive Drug Research Committee (RDRC)

Institutional Biosafety Committee (IBC)

QUESTION	ANSWER
I am submitting an application for a Principal Investigator and when I try to enter their information, it is not populating. What should I do?	Please reach out to Biosafety@utsouthwestern.edu for assistance with updating the system records.
I am submitting an application for a Principal Investigator (PI), how do I know the submission has been received?	Once an applicant submits an application, the PI will receive a system notification indicating that a registration has been submitted on their behalf. The PI needs to log into the system and certify the submission. Once the submission is certified, the certification status will change from "Pending" to "Completed."
How long is the IBC review period?	• Human Subject Gene Transfer registration (investigational drug). After an application has been received, the review period is 60 – 90 days. • Human Subject Human Materials registration (sample collection only). After an application has been received, the review period is 15 – 45 days.
When will an approval letter be available?	Approval letters will be available in the system no later than 5 business days after the IBC authorizes the registration.

For any other IBC questions, email Biosafety@utsouthwestern.edu.

Office of Clinical Trial Management: Performance Site Review (PSR) Form

QUESTION	ANSWER
Will this form replace the Children's and Parkland performance site review form as well?	No, this new PSR form is only applicable for clinical research activities done on UT Southwestern premises. This includes hospital-based, ambulatory, and academic spaces. Children's will continue to use their current PSR form in Velos. Parkland has a separate form in REDCap.
When should I submit the UT Southwestern performance review form?	To ensure timely review of your study and Greenlight activation, you should submit your PSR form to the Office of Clinical Trials Management (OCTM) when IRB submission is completed and IRB is at "Waiting assignment stage" in Velos. Our review process also uses information from the cost coverage analysis (if applicable). Therefore, timely submission of the cost coverage analysis will further enable a faster review completion timeline.
My study is conducted by UT Southwestern personnel, but all study related procedures will be performed at Children's Medical Center or Parkland Health and Hospital System, do I still need to submit for UT Southwestern performance site review?	If UT Southwestern is selected as a site in eIRB, limited entry into the PSR form is required. In the scenario described, select UT Southwestern as a site in eIRB, which will cue up the UT Southwestern PSR form. If no study-related activities will be conducted at UT Southwestern in this scenario, answer only the first question on the form and submit. OCTM will review the submission and if no study- related activities will occur on UT Southwestern premises, the study will be labeled a": "Performance Si–e - Approval Not Required." This designation will NOT trigger "Greenlight".
Can I leave a question blank? Is entering 'N/A' necessary?	If a question does not apply it can be left blank. There is no need to enter 'not applicable.'
Why does "Section 2: Participants" only ask for the number of subjects at UT Southwestern?	We are reviewing and approving only activities conducted at UT Southwestern, therefore only volunteers who enroll and participate in the study at UT Southwestern need to be listed. If your study is also conducted at one of our affiliated institutions, performance site approval is required by those institutions. Even if the only activity at another site is subject recruitment, performance site approval is still required.
Is the location given in "Section 3" the only approved location for the study?	YES, you are only approved to perform the tasks noted in the respective areas. Should this information change during the conduct of the study, an updated form should be submitted for review and approval.

What if more procedures are needed than will fit in the space provided?	If your study requires more procedures than the form allows, place list all remaining procedures in the last text field.
What if my study uses an ancillary service not available in the form?	For ancillary services not provided in the form you may list the service/test and the detailed location in the Procedure portion of "Section 3: Location" (Example: Pulmonary function test, echocardiogram, dermatology evaluation, etc. would be listed in this section)
What if coordinators do not have knowledge of where a procedure should be conducted?	Please provide as much detail about the procedure as possible and OCTM will assist the team in finding the ancillary service that can perform the procedure.
What if the exact procedure is not known ahead of time (for example: biopsy of tumor deposit – cannot predict where the tumor deposit might be located).	Please provide as much detail as known about the procedure in case, and preferably also list the most commonly anticipated situations
Isn't asking for the number of tests per participant in the entire study misleading as adverse events would cause changes to this number?	Please list all procedures along with the number of times it will be performed as described in the protocol. We understand that unforeseen events can occur which might require additional testing on a case-by-case basis.
Do ALL IATA-certified study team members need to be listed?	List only the names of the individuals who are assigned to ship samples for the respective study.
Should all study-related tests and procedures be listed on the PSR form, or only those billed to research?	You should ONLY list services that are for research-only and thus billed back to the research team. Services billed to insurance/patient (standard of care) should NOT be listed on this form.
Why does the Radiology section not ask for the imaging tests requested?	The reviewers in the Department of Radiology use the Imaging manual and Study Protocol to determine the specific study needs. Radiology staff will also consult with you if questions arise.
In "IP maintenance" section, what if coordinator does not know the intensity?	Please provide your best estimate based on your understanding of the study. The team reviewing this section will adjust the intensity level if needed.
What does the institutional review process entail?	The institutional review entails several different important aspects geared to ensure your study is conducted in a safe environment and that all services involved are aware and available to help you perform your study. Examples of our review include: 1. confirm that all research personnel listed on your protocol have completed their annual research credentialing; 2. review of your completed PSR form and study protocol to determine what UT Southwestern resources and services will be needed to conduct your study. Those services will be notified to perform a review and ensure

	they can conduct your research according to the protocol; 3. ensure the location of each research volunteer encounter is adequate and safe; 4. coordinate with the cost coverage analysis team to ensure all research-only procedures/services are correctly identified; 5. create a summary of all approved activities for the respective study, along with respective identifiers (CPT codes) or anticipated cost.
How quickly can I expect to have my study approved?	All studies are reviewed by OCTM as soon as they are submitted. Studies which involve minimal UT Southwestern resources (i.e., chart reviews, retrospective studies, observational studies with minimal testing, etc.) undergo a fast-track review and approval (approximately one week). More complex studies which require review, approval, and coordination among multiple ancillary services may take up to 3-4 weeks to complete review. OCTM meets twice a month with a review committee comprised of our Medical Director, Associate Dean of Clinical Research, and representatives from various ancillary services to facilitate the review and coordination among ancillary services and minimize time to approval for your study.
If the performance site form is not submitted until after IRB submission, will it delay receipt of ancillary pricing?	The new performance site review process will have an earlier timeline during the research review cycle, as it is a required component of "Greenlight". Institutional research prices (including the CRU and IDS pricing menu) are published in the Velos library. Study teams should use these published prices for the purpose of budget negotiations. To obtain general information about special research- only testing/procedures not listed in Velos, or if you have specific questions about the availability or feasibility of a test/procedure, please reach out either to OCTM or the respective ancillary service to discuss your project. Once you have a final protocol and you are committed to conducting the study, early submission to IRB and Performance Site Review is key to obtaining "Greenlight" in a timely fashion.
Will pricing still be available in Velos?	Yes, the Velos price library is the best place to obtain the most current research prices approved by UT Southwestern. According to UT Southwestern policy, prices for research-related CPT codes should be taken directly from Velos.
In Section 3: "Location" of the form, how is Cancer Center defined and what areas does it include?	This section is focused on where study-related activities will be physically conducted. The Cancer Center option is for activities that will physically occur on Simmons Comprehensive Cancer Center (SCCC) premises, e.g.,

	main SCCC clinics on campus or outlying clinics owned by SCCC.

For any other Performance Site Approval questions at UT Southwestern, you may call 214-648-7553 (OCTM), email OCTM@UTSouthwestern.edu, or attend OCTM's Open Office Hours.

The weekly Virtual Open Office Hours Sessions are Thursdays from 10:00am – 11:00am. Request the virtual meeting link as an outlook calendar invite by contacting the OCTM via email.

The OCTM also shares Virtual Open Office Hours with the HRPP on Tuesdays from 10:00am – 11:00am. To get the Zoom link to the Tuesday sessions, go the HRPP website and subscribe to the listserv listed on the website: Human Research Protection Program (HRPP): UT Southwestern, Dallas, Texas.

Protocol Review and Monitoring System (PRMS)

QUESTION	ANSWER
Does my study require Protocol Review and Monitoring Committee (PRMC) review in eIRB?	To determine whether PRMC review is required, we must first determine if the study is, "Cancer Related." Cancer-related outcomes or other study endpoints may reflect clinical treatment or quality of life, change in attitudes/beliefs or behaviors, or healthcare delivery for either solid tumors or hematology/hematologic malignancies. Such studies can occur at any point along the cancer care continuum, including screening and early detection, diagnosis and treatment including palliation and symptom management, through survivorship, as well as end of life and hospice. These studies then may include enrollment or measurements of any of the following: 1) cancer patients, their caregivers or relatives 2) or cancer clinical care team members, 3) or individuals targeted for cancer prevention activities including lifestyle change, 4) or the assessment of cancer epidemiologic, imaging, or biological markers. Thus, to the question, "Are the primary or secondary outcomes of the study aims cancer-related?" if your study meets this criterion answer "Yes" to question *7.7 in the eIRB Smartform when completing the study submission questionnaire. Studies that do not meet this criterion should answer "No" to question *7.7 in the eIRB Smartform when completing the study submission questionnaire.

For any other PRMC questions, please refer to:

https://www.utsouthwestern.net/intranet/departments-centers/cancer/research/prmcguidance.html.

ClinicalTrials.gov Support Program FAQs	
QUESTION	**ANSWER**
Who should register the study in ClinicalTrials.gov?	Regulation requires that the "Responsible Party" registers and submits results for "applicable clinical trials" (ACTs) and NIH funded clinical trials. The International Committee of Medical Journal Editors (ICMJE) publication policy also requires registration in ClinicalTrials.gov as a condition of consideration for publication.
I plan to submit Medicare and/or Medicaid claims for my study. Is Clinicaltrials.gov registration still required?	If you plan to submit Medicare or Medicaid claims to CMS (Centers for Medicare and Medicaid Services), then registration to ClinicalTrials.gov is required.
My study's funding agency has requested that we register the study.	Follow the funding agency's requirements and register. For example, any private organization may request this, such as the Gates Foundation, Wellcome Trust, Global Alliance, etc.
How do I determine who is the Responsible Party for a study?	The Responsible Party is defined as an individual who: • is responsible for conducting trial, • has access to & control over the data from clinical trial, • has right to publish results of the trial, AND • has ability to meet all the requirements. *For a study conducted under IND/IDE, regulation requires "Sponsor Investigator" (IND/IDE holder) to register and submit results in ClinicalTrials.gov.
When should ClinicalTrials.gov registration be done?	We recommend the Responsible Party to initiate ClinicalTrials.gov registration before eIRB study submission because an NCT # is required for NIH-funded clinical trials and applicable clinical trial protocol activations.
How long will it take to register a study in ClinicalTrials.gov?	NIH estimates registration can take up to 10 hours, depending on the complexity of the study and the number of pre-specified outcome measures.
When will the NCT number be assigned?	Approximately 2 to 5 business days after the record is released
Can I update outcome measures after the study has started?	To avoid the appearance of outcome switching (e.g., publication bias), we recommend keeping the original outcomes as is and add explanations in the Outcome

	Measure Description section about the changes in outcome measures (e.g., “This outcome will not be collected as the test is no longer available”).
Will results posting on ClinicalTrials.gov be considered “s "prior publication"?	No, posting of tabular results data to ClinicalTrials.gov is not considered prior publication per International Committee of Medical Journal Editors (ICMJE) policy
Which trials must post consent forms and when?	Clinical trials funded or conducted by a Common Rule department or agency, that were either IRB approved on or after January 21, 2019, or voluntarily transitioned to the Revised Common Rule requirements, must post a consent form after recruitment closes, and no later than 60 days after the last study visit by any subject.
Can I delete a record from the ClinicalTrials.gov public website?	No, once a study earns the NCT#, it cannot be deleted
Do I need to submit statistical test results?	In general, statistical test results are optional, but may be required if pre-specified in protocol as primary/secondary outcome measures.
Can I get an extension for results reporting?	An extension may be permitted if the request is submitted prior to the results reporting due date (i.e., day before) with a ***valid*** reason. For guidance, reach out to the RSO.
Do I need to report results when the study was terminated?	Results reporting required for a terminated study depends on the overall recruitment status and whether data were collected for the purpose of study. For those studies terminated prematurely but data were collected, then results reporting of available data are required. Whereas those studies withdrawn before stating enrollment, no results are required to be reported because there is no reportable data.
Sponsor Investigator Support Program FAQs	
QUESTION	**ANSWER**
How do I know whether an IND or IDE is required for a study?	The Regulatory Support Office (RSO) provides comprehensive information to help determine whether or not an IND or IDE is needed for a proposed study.
Do I need an IND if I use a lawfully marketed drug for an unlabeled indication?	If you prescribe a marketed drug to treat a patient for an unlabeled indication (i.e., off-label use), an IND is not required because this use is considered to be within the scope of medical practice and not a clinical investigation.
Can a patient be treated with an investigational product outside of a clinical trial?	Yes, a treating physician can request a single patient Expanded Access IND/IDE to the FDA. The goal of

	Expanded Access is treatment as opposed to research. Approval can be expedited in emergency situations.
Who is considered the sponsor of an IND or IDE study?	The sponsor is the individual who initiates the IND or IDE and is responsible for both the oversight of the clinical trial (or Expanded Access treatment IND or IDE) and all communications with the FDA.
What is a Letter of Authorization (LOA)?	An LOA is a permission letter from the sponsor (i.e., manufacturer of the investigational product) allowing the FDA to cross-reference confidential information of the sponsor's existing IND on file to support your new IND application. Such confidential information may include: • Description of the facility where the drug is manufactured • Chemistry, Manufacturing, and Controls • Pharmacology, Toxicology information • Labeling • Previous Human Experience
What is the difference between an abbreviated IDE and an IDE?	An abbreviated IDE is required for non-significant risk device studies and overseen by the IRB. An IDE is required for significant risk device studies and overseen by the IRB and FDA.
Do I first submit to the IRB or FDA when submitting protocol modifications?	FDA and IRB submissions may occur in any order. However, we recommend to first obtain the IRB approval so that the sponsor can include the IRB approval letter in the protocol amendment application to the FDA.
When is an IND Annual Report/IDE Progress Report is due?	The IND Annual Report is required to be submitted within 60 days of the one-year anniversary of the IND effective date. The IDE Progress Report is required to be submitted at regular intervals, but no less than yearly for the IDE.

For additional questions and/or to request a booking with the RSO, please go to: Regulatory Support: Human Research Protection Program (HRPP) – UT Southwestern, Dallas, TX.

Tips and Tricks for Credentialing

- **Each link is unique to the individual –** please do not forward to other researchers.
- **Only apply for sites at which you are conducting research** – the team will review the performance sites approved for your eIRB studies. You may end up supplying extra, unnecessary information for sites which you are not working at.
- **Only apply if you are already named on an active eIRB study**
- **Ensure you have all documents ready before starting your application –** complete applications are taking 1-2 business days to be completed, incomplete applications will not be accepted.

QUESTION	ANSWER
What if a researcher already has CITI GCP, HSP etc. training from another institution, but we are unable to merge them/apply them to UTSW?	Merge Duplicate Accounts • If you would like to merge two learner accounts, please send an email to support@citiprogram.org and include all the information below: • Your name • The name of your institution • The member ID number, last name, first name, and username of the learner whose account you wish to keep • The member ID number, last name, first name, and username of the learner whose account you wish to merge
CITI TRAINING SUPPORT	Send technical queries to support@citiprogram.org or call (US toll free): 888-529-5929 Send billing/financial queries to admin@citiprogram.org or call (US toll free): 888-529-5929 For international content or languages availability contact support@citiprogram.org or call (outside US): +1-305-907-3100
What is the process to update CITI training or start as a new researcher?	To be added to an approved research study, complete online training through CITI: https://www.citiprogram.org/default.asp?language=english The following are recommended: a. Human Subjects Protection b. HIPAA Research Rule c. Good Clinical Practices

Can you send the TB questionnaire since it is not available in Readyset to complete?	Please reach out to Occupational Health to have Readyset to be re-initialized so you can complete the TB questionnaire and send it in.
Can I wait to get my Life support certification before completing my credentialing packet?	Please register in Taleo for the next available class and upload the documentation of your registration into your REDCap survey. This will not hold up your credentialing, but it is required to be completed as soon as possible. Please submit your packet for review.
How do I register for Phlebotomy training?	The class you sign up for is “Phlebotomy Class for Ambulatory Staff” in Taleo, but this is just to reserve the in-person class. Once you are approved, you will be assigned a module to complete in Elsevier prior to the class titled "AMB Blood Specimen Collection: Venipuncture Vacuum Extraction Method". You will be asked to have a preceptor to check you off after you attend the class. Please register in TALEO for the “Phlebotomy Class for Ambulatory Staff”, but this is just to reserve the in-person class. Once you are approved you will be assigned a module to complete in Elsevier prior to the class titled "AMB Blood Specimen Collection: Venipuncture Vacuum Extraction Method". You will then be asked to have a preceptor to check off your skills after you have attended the class.
Who do I contact if I have problems accessing Taleo?	Please reach out to Paul Scott or email Taleolearn@UTsouthwestern.edu for further assistance.
How do I start the credentialing process for non- UT employed study personnel?	Obtain a POI#. Start here: HRISServiceCenter HRISServiceCenter@UTSouthwestern.edu Complete all required CITI trainings (see above) To be added to an approved research study, complete our research credentialing After completion of CITI training- NON-Physicians (Unless not MSO credentialed) who will have patient contact or review PHI are required to complete Research Credentialing in a timely fashion.

For any other Credentialing questions, contact Research Staff Credentialing at: utswresearchcredentialing@utsouthwestern.edu.

Radioactive Drug Research Committee (RDRC)

QUESTION	ANSWER
Is a separate IND needed to use a radioactive drug as a research tool in studies being conducted under an existing IND for therapeutic drug development? For example, could a radioactive drug be used to image a nonradioactive therapeutic drug's effects on an organ?	No, a separate IND is not needed for the radioactive drug if there is an existing IND and that IND is amended to label the drug with a radionuclide. This may be preferred because the IND already exists. An alternative approach would be to conduct the study using the subject drug separately under the oversight of an RDRC if the data to be collected are basic science information and the study meets all of the conditions of § 361.1. However, this assumes no pharmacologic effect for the study drug, and monitoring a therapy drug would most probably involve using a therapeutic dose, which would disqualify this from an RDRC study. If the RDRC conditions were met, and the studies were conducted under RDRC review, the results of the radioactive drug studies should be included in the IND of the nonradioactive drug that is being developed.
Is an IND needed if research using a radioactive drug starts out as basic science but then changes to clinical research?	Yes, an IND would be needed when research goals change to study the clinical safety or effectiveness of the radioactive drug. For example, the initial investigations to demonstrate the localization of a radioactive drug to a particular organ or fluid space and to determine the kinetics of that localization could be considered basic research. If all other conditions of § 361.1 were met, those investigations could be conducted under an RDRC. If and when the basic science research evolves into a more formal clinical trial that expands beyond the conditions of § 361.1, it would have to be conducted under an IND. The IND could be submitted at the time that the basic research of the radioactive drug begins under § 361.1.
I am not sure whether my research will evolve into drug development for use in a clinical setting. Should I submit an IND?	Yes. While early research objectives may be basic research and may or may not evolve into a formal clinical trial for safety and/or efficacy, if there is doubt as to whether the research is still basic science research, FDA recommends that the drug be studied under an IND.
If basic research with a radioactive drug does not meet RDRC conditions for pharmacological activity and/or radiation dose limits, but the radioactive drug is a simple, commonly used compound, is an IND needed?	Yes. If basic research with a radioactive drug does not meet all the conditions under § 361.1, including limits on the pharmacological and radiation doses, the research may not be conducted under an RDRC and is subject to the IND regulations. However, some clinical investigations of a drug product that is lawfully marketed in the United States may be exempt from IND

	requirements under certain conditions (see § 312.2 (b), Exemptions).
If research is being conducted to identify a radioactive drug to eventually be used in human therapy, diagnosis, or prevention trials, should the investigator begin by submitting an IND, or should an IND be submitted at the conclusion of the basic science studies?	For the initial basic science studies meeting requirements of § 361.1, the investigator has the choice of conducting the studies under the RDRC or under an IND. However, after these initial basic science studies are complete, an IND must be submitted to conduct clinical trials to determine the safety and effectiveness of the radioactive drug. One type of IND that is intended to be simpler than the traditional IND, the exploratory IND,** involves limited human exposure and may require less preclinical support than traditional IND studies. ** See the guidance for industry, investigators, and reviewers on Exploratory IND Studies (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf). Please note that the Exploratory IND guidance does not apply to all drugs regulated by CDER and does not apply to CBER regulated drugs.
Can I use a radioactive biological product as a radioactive drug under an RDRC?	Yes. The term radioactive drug includes radioactive biological products labeled with a radionuclide (21 CFR 310.3(n) and 600.3(ee)). Therefore, basic research studies with a radioactive biological product may be conducted under RDRC review if they meet all the requirements set forth in § 361.1. However, biological products (e.g., monoclonal antibodies and therapeutic proteins such as cytokine, interferon, interleukin, and enzymes) that are immunogenic proteins could potentially produce an antigenic response. Therefore, we recommend that only basic research with radioactive biological products that have been shown to have no immune response be conducted under § 361.1.
Does an existing IND for a nonradioactive investigational drug need to be amended if the drug is labeled with a radionuclide?	It would be preferable for an existing IND to be amended if the drug is labeled with a radionuclide, but this may not be required under certain circumstances. It would not be necessary to amend an existing IND if the investigator wanted to conduct the research under an RDRC, the radioactive form of the investigational drug met all conditions of § 361.1, and the research was reviewed and approved by the RDRC. The results of the research should be submitted to the IND. If the RDRC requirements were not met (e.g., the research was not basic science in nature, or the pharmacological or radiation doses were not within the limits specified in § 361.1), an IND would be required. In that case, to use the

	radioactive form of the investigational drug, the existing IND would have to be amended, or a new IND submitted.
I have an unapproved radioactive drug that I want to use to monitor the progress of therapy in patients who are given various therapeutic drugs. Do I need to submit an IND?	Yes. Because the imaging results from the radioactive drug will provide immediate diagnostic information about patients, this is not considered basic research and you will need an IND.
Can I use an unapproved radioactive drug if I use it for an occasional patient who may be difficult to diagnose, and I'm exploring whether this test is useful?	This type of study requires an IND because you cannot use an unapproved radioactive drug for diagnosis on humans without an IND.
What is the difference between an RDRC and a Radiation Safety Committee?	A Radiation Safety Committee (RSC) is mandated by various Federal, state, and local agencies for the purpose of ensuring the safety of an institution's overall program for the use of radioactive materials and radiation producing equipment. An RDRC is mandated and approved only by FDA for the specific purpose of approving and monitoring basic human research studies using radioactive drugs under the conditions set forth in § 361.1. A medical institution may involve its RDRC in other matters, such as the review of institutional radiation safety issues or the review of research conducted under an IND, but FDA regulations do not require that RDRCs perform such activities.
Will my study need to be approved by both my RDRC and IRB?	Yes. Section 361.1(d)(9) requires that all research on human subjects under an RDRC also have IRB approval.
If my study meets all the requirements in § 361.1, do I need an IND?	If your study meets the requirements of § 361.1 as determined by your RDRC, this means your study does not need an IND. However, your RDRC may prefer that your study be conducted under an IND for a variety of medical, ethical, or legal reasons, and may not approve your study under the RDRC authority
If the RDRC does not approve my study, do I need an IND?	If your study does not meet the requirements of § 361.1 as determined by your RDRC, your study must be conducted under an IND unless it meets the conditions for IND exemption (§ 312.2(b)).
Can I enroll pregnant women in my study for my basic research under an RDRC?	No. For a more detailed discussion please see section III.B, What Are the Study Criteria for Research Conducted Under an RDRC, Human Research Subjects, (3) Women of childbearing potential, for additional information. (https://www.fda.gov/media/76286/download).
Are studies involving pediatric subjects appropriate under an RDRC?	Although RDRC research subjects generally must be 18 years of age or older, exceptions are permitted in special situations. Please refer to section III. B, What Are the

	Study Criteria for Research Conducted Under an RDRC, Human Research Subjects, (4) Pediatric subjects, for additional information.
Under what circumstances can I use doses of a radioactive drug that have a pharmacological effect for studies of basic research, metabolism, and pharmacokinetics, and not need an IND for the radionuclide study?	There are no such circumstances. If your radioactive drug has a clinically detectable pharmacologic effect, your studies will not meet the requirements of § 361.1, and you will need an IND.
If the mass dose of the unapproved radioactive drug I'm planning to study has a pharmacological effect, what should I do?	You will need to submit an IND. Contact the RSO for assistance.
Must I conduct dose-response studies to support no clinically detectable pharmacological effect?	No, there is no requirement for a formal dose-response study to define the lower threshold for a clinically detectable pharmacological effect. For example, if the circulating blood levels or excretion rates of endogenously produced substances are well known, it may be possible for the RDRC to conclude that some small fraction of these levels or rates of administration (e.g., administration over a given interval of a low percentage of amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Or, if large amounts of substances such as amino acids or sugar are regularly consumed as foodstuffs, it may be possible for the RDRC to conclude that a small amount of it (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity.
How do I determine the actual radiation dose for each individual subject?	In many cases, the actual individual radiation dose can only be estimated using standard adult and child reference models published by organizations such as the Society of Nuclear Medicine's (SNM) Medical Internal Radiation Dosimetry (MIRD) Committee, the British Health Protection Agency (formerly the National Radiological Protection Board (NRPB)) for x-ray sources, including CT, and the FDA for conventional x-ray. FDA believes that the determination of radiation dose to specific tissue or organs using currently accepted methods, such as the system set forth by the MIRD Committee, or the system set forth by the International Commission on Radiological Protection (ICRP), is sufficiently accurate for estimating radiation risk from radiolabeled drugs used in RDRC research. Although there are inherent limitations because of differences

	between standard reference models and actual human subject size and organ geometries, the risks associated with these low radiation doses are sufficiently low that the uncertainty associated with these estimates is acceptable for RDRC research. ***However, these methods alone are insufficient for the determination of radiation doses for radiotherapeutic purposes. The variation and uncertainty in patient specific anatomies, and the complexity of the pharmacokinetics and dosimetries, preclude using such standard models for radiotherapeutic purposes.***
How do I report the radiation dose for each individual subject in my annual report to FDA?	Radiation dose must be reported as the organ dose for select organs and as a whole body dose, as specified in § 361.1(b)(3)(i) (see Table 1, Limits on Radiation Dose for Adults, of this guidance). Since the promulgation of § 361.1 in 1975, the ICRP has defined effective dose (E) to equate partial body doses to a whole body dose. Therefore, the whole body dose may be reported as E in the annual report to FDA using the most current tissue weighting factors published by the ICRP. However, individual organ doses must still be reported. Administered radioactivity is not radiation absorbed dose.
What units should I use for reporting radiation dose in my annual report to FDA?	FDA prefers that radiation be reported using the International System of Units (SI), Becquerels for radioactivity, Gray for the physical concept of dose, and Sieverts for the biologically equivalent dose. **Units of Radioactivity** Becquerel (Bq) = 1 disintegration per second Curie = 3.7×10^{10} disintegrations per second = 3.7×10^{10} Bq 1 mCi = 37 MBq **Units of Physical Absorbed Dose** Gray (Gy) = 1 joule of energy absorbed per 1 kilogram of mass Gray = 100 rads mGy = 100 mrads **Units of Biologically Equivalent Dose** Sievert (Sv), the biologically equivalent dose, obtained when the physical dose, in Gray, is modified by a radiation weighting factor, wR, previously known as a quality factor, which varies depending on the type and energy of the radiation. This is usually 1 for gamma, x-ray, and electron energies, but varies significantly for

	some particulate radiations such as alpha and neutron radiations. Sievert = 100 rems mSv = 100 mrem Since the radiation weighting factor, w_R, is usually 1 for gamma and x-ray photons, typically the primary types of radiation used in medicine, the terms are often used interchangeably. A 10 mGy (1 rad) x-ray or gamma ray dose is sometimes referred to as a 10 mSv (1 rem) dose. A 10 mGy (1 rad) dose of alpha or neutron radiation will result in a much higher equivalent dose, depending on the quantity of w_R. If w_R is 10, then the corresponding equivalent dose will be 10 times the absorbed dose in Gy (rads) (e.g., 1 Gy (100 rad) = 10 Sv (1000 rem)).

Please note that the information above was obtained from the FDA *Guidance for Industry and Researchers – The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application* published in August 2010 (https://www.fda.gov/media/76286/download).

Please refer to the RDRC website for additional information and guidance: https://www.utsouthwestern.net/intranet/administration/safety/safety-programs/radiation/rad-subcommittees/radioactive-drug-research-committee.html.

For guidance on the Investigational New Drug (IND) process, please reach out to the RSO: https://www.utsouthwestern.edu/research/hrpp/regulatory-support/

E. References

The content of this handbook was culled from multiple sources that include academic publications focused on clinical research topics, government websites, contributions from departments and offices within the University of Texas Southwestern Medical Center, among others. This section has organized all major sources of contributions into the following groups: Bibliography, FDA Guidance Documents and Websites, NIH Guidance Documents and Websites, and Other Website Resources.

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FDA Guidance Documents and Websites

- http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
- FDA Guidance on Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects
- FDA Glossary (Drugs): http://www.fda.gov/drugs/informationondrugs/ucm079436.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: https://www.fda.gov/media/72267/download
- Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring, August 2013: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring
- Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UC M227351.pdf
- FDA Code of Federal Regulations: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
- DRAFT Guidance for IRBs, Clinical Investigators and Sponsors: Informed Consent Information Sheet: http://www.fda.gov/RegulatoryInformation/Guidances/ucm404975.htm
- FDA Guidance on Safety Reporting for INDs and BA/BE (Bioavailability/Bioequivalence) Studies http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm2 27351.pdf
- September 2013 FDA guidance titled “Electronic Source Data in Clinical Investigations”, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UC M328691.pdf
- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies: Significant Risk and Nonsignificant Risk Medical Device Studies - Information Sheet (fda.gov)

- FDA: The Drug Development Process: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process
- FDA: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry: Guidance for Industry (fda.gov)
- FDA: A Guide to Informed Consent: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guide-informed-consent#process
- Corrective and Preventive Actions (CAPA): https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/corrective-and-preventive-actions-capa
- Electronic Source Data in Clinical Investigations: Guidance for Industry: Electronic Source Data in Clinical Investigations | FDA

NIH Guidance Documents and Websites

- NIH Glossary & Acronym List: http://grants.nih.gov/grants/glossary.htm
- NIH: https://www.nih.gov/
- NIH Data Safety Monitoring Plan requirements: http://www.nlm.nih.gov/ep/dsm.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: https://www.nimh.nih.gov/funding/clinical-research/data-and-safety-monitoring-plan-writing-guidance
- 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
- NIH Data Quality Management in Clinical Research: https://oir.nih.gov/system/files/media/file/2021-08/data_quality_management-2015_05_15.pdf?iOS=
- NIH Certificate of Confidentiality: http://grants.nih.gov/grants/policy/coc/index.htm
- NIH National Library of Medicine: https://www.ncbi.nlm.nih.gov/
- Final NIH Policy for Data Management and Sharing: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-013.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Protecting Privacy When Sharing Human Research Participant Data: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-213.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Responsible

Management and Sharing of American Indian/Alaska Native Participant Data: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-22-214.html

- Supplemental Information to the NIH Policy for Data Management and Sharing: Selecting a Repository for Data Resulting from NIH-Supported Research: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-016.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Allowable Costs for Data Management and Sharing: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-015.html
- Supplemental Information to the NIH Policy for Data Management and Sharing: Elements of an NIH Data Management and Sharing Plan: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-014.html

Other Website Resources

- ClinicalTrials.gov Glossary: https://clinicaltrials.gov/ct2/about-studies/glossary
- The full DHHS organizational chart: http://www.hhs.gov/about/orgchart/
- UT Southwestern Human Research Protection Program (HRPP) Website: https://www.utsouthwestern.edu/research/hrpp/
- UTSW Institute for Clinical and Translational Research: https://www.utsouthwestern.edu/research/ctsa/
- UTSW Internal Webpage: https://www.utsouthwestern.net/
- UT Southwestern, Sponsored Programs Administration: https://www.utsouthwestern.edu/employees/spa/
- The Belmont Report: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.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
- OHRP Guidance on Withdrawal of Subjects from Research: Data Retention and Other Related Issues: https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/subjectwithdrawal.pdf
- National Center for Advancing Translational Sciences (NCATS): https://toolkit.ncats.nih.gov/glossary/endpoint/
- International Conference on Harmonization Good Clinical Practice: ichgcp.net
- OHRP Tips on Informed Consent: (http://www.hhs.gov/ohrp/policy/ictips.html
- UT Southwestern Health Information Portability & Accountability Act (HIPAA): https://www.utsouthwestern.net/intranet/administration/compliance/hipaa-

privacy/

- Safety Profiler/Common Terminology Criteria for Adverse Events (CTCAE) maintained by the NCI: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
- American Cancer Society: Types and Phases of Clinical Trials | What Are Clinical Trial Phases? (cancer.org)
- Centers for Medicare and Medicaid Services: Code of Federal Regulations | CMS
- Centers for Disease Control and Prevention: https://www.cdc.gov/ncbddd/autism/index.html
- National Institute on Deafness and Other Communication Disorders: What Is Epidemiology? | NIDCD (nih.gov)
- National Cancer Institute: https://www.cancer.gov/
- Disability Rights Texas: Legally Adequate Consent (Posted on August 16, 2018): https://disabilityrightstx.org/en/handout/legally-adequate-consent/
- Collaborative Institutional Training Initiative (CITI) Program: Research, Ethics, and Compliance Training | CITI Program.

F. Additional Contributors

The following individuals created, reviewed, edited, and/or contributed information, including original recording content, that were utilized in the Clinical Research Foundations training program. The information produced for the video series (included in both the CITI Clinical Research Foundations course as well as the training website platform) also provided content for this handbook.

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