PRINCIPAL INVESTIGATOR RESPONSIBILITIES FOR BIOMEDICAL RESEARCHERS

INTRODUCTION

The purpose of this module is to provide a basic understanding of the responsibilities of the principal investigator involved in the conduct of biomedical research. By the end of this module you will be able to describe the role of the Principal Investigator, and the responsibilities that accompany that role.

DEFINITIONS

Biomedical Research: The *New Jersey Association for Biomedical Research defines biomedical research* as "the broad area of science that looks for ways to prevent and treat diseases that cause illness and death in people and in animals." This general field of research includes many areas of both the life and physical sciences.

Principal Investigator: The term Principal Investigator (PI) is used to identify a researcher with primary responsibility for a research project.

WHO CAN SERVE AS THE PI?

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

NOTE: Having PI status on a grant application is not the same as having PI status for the purposes of human subjects protocols reviewed by an IRB

INVESTIGATOR RESPONSIBILITIES

This section will describe the responsibilities of the PI to ensure the protection, rights and well-being of subjects.

Responsibilities of the PI include, but are not limited to:

1. Comply with the principles of the Belmont Report and adherence to the regulations outlined in the Common Rule and other applicable regulations, such as the Food and Drug Administration (FDA).
2. File and update Outside Activities Reports, disclosing relevant potential financial conflicts of interest to the IRB, and following any management plans for human subjects research issued by the campus Conflict of Interest Committee.
3. Provide adequate training to and oversight of study personnel and, in the case of clinical research, ensuring protocol procedures comply with Good Clinical Practice requirements.
4. Obtain written documentation of IRB approval or exemption of the study prior to initiating human subjects research.
5. Ensure that legally effective informed consent has been 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).
6. Ensure permission for the use and disclosure of protected health information is obtained in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, if the research staff are within the Health Care Component or part of the Affiliated Covered Entity.
7. Ensure compliance with the conditions of IRB approval, 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, monitor for changes that could alter the exemption determination and consulting with the IRB as necessary.

8. Obtain IRB approval prior to the implementation of changes of protocol and promptly report changes of protocol.
9. Submit continuing review progress report(s) in a timely manner.
10. Report unanticipated problems to the IRB.
11. Report noncompliance to the IRB.
12. Ensure adequate medical oversight for clinical trials.
13. Ensure adequate records are kept to document study procedures and adherence with the IRB-approved application and protocol, as well as ensuring the records are retained and accessible for the required retention period.
14. Maintain adequate records regarding the recept, use and disposition of investigational drugs, biologics or devices used in a research study.
15. Register studies and provide updated information to ClinicalTrials.gov, when required.
16. Ensure that additional procedures are in place for investigator-initiated, multi-center studies.

1. COMPLIANCE WITH APPLICABLE REGULATIONS, LAWS, AND POLICIES GOVERNING HUMAN SUBJECTS RESEARCH

For UW-Madison to receive federal funding to support human subjects research, the institution must have a Federalwide Assurance (FWA) with the U.S. Department of Health and Human Services (DHHS), Office for Human Research Protections (OHRP). The FWA states that **all human subjects research activities will be guided by the ethical principles** outlined in the Belmont Report and that federally supported research activities comply with the Common Rule. Investigators should become familiar with these principles and regulations to ensure that their research complies with them. Failure to comply with these principles can place both subjects and the institution at risk.

Investigators are required to comply with the FDA regulations when the product

under investigation is intended to support an application for FDA approval of products including, food, certain dietary supplements, infant formula, a food or color additive, a drug, a biologic or medical device for human use, or an electronic product.

2. CONFLICT OF INTEREST POLICY

Investigators are required to file a UW-Madison Outside Activities Report/Disclosure prior to the submission of a protocol to an IRB for review and are responsible for keeping these disclosures current. Additionally, investigators must comply with the campus Conflict of Interest policies related to human subjects research, including disclosing potential conflicts of interest to the IRB and abiding by any management plans issued by the campus Conflict of Interest Committee.

3. OVERSIGHT AND SUPERVISION

Although PIs may delegate certain research-related tasks to other members of the research team, they retain **ultimate responsibility** for the conduct of the study. The PI is the person ultimately responsible for the legal and ethical conduct of the study in accordance with the protocol, signed investigator agreements, and applicable regulations. The PI must be qualified by education, training, or experience to assume this responsibility.

Investigators are responsible for ensuring staff are qualified to perform their delegated tasks, and certifying that study personnel are aware of the regulations governing human subjects research and **understand and adhere to the IRB-approved research protocol**.

For clinical research studies involving investigational drugs, biologics, or devices,

PIs are required to personally conduct or supervise the investigation and comply with the IRB-approved protocol.

In the case of clinical research, the PI must ensure all members of the research team are trained on, and follow Good Clinical Practice (GCP) guidelines, an international ethical and scientific quality standard for designing, conducting, monitoring, auditing, recording, analyzing and reporting trials that involve the participation of human subjects. Compliance with these standards provides assurance that the rights, safety, and well-being of human subjects are protected and the integrity of the data collected.

Certain tasks may be delegated to qualified members of the research team, but the responsibility for ensuring tasks are performed in accordance with the protocol and regulations is the PI's, and cannot be delegated.

The PI should ensure that a member of the research team to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task(s).

FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but **do not permit clinical investigators to delegate their general responsibilities** to CROs or site management organizations, sub-investigators, or other members of the research team.

PIs must also ensure that adequate resources are available for the conduct of the study.
The investigator should have sufficient time and adequate resources to properly and safely conduct and complete the trial within the agreed trial period.

4. OBTAINING IRB APPROVAL OR EXEMPTION TO

CONDUCT HUMAN SUBJECTS RESEARCH

Before initiating a study, a PI must obtain approval by the IRB to conduct human subjects reasearch or a determination by the IRB that the study is exempt from IRB review.

To be considered "human subjects research", a project must meet both the federal definitions of "research" and "human subjects".

Research is defined under the Common Rule as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

Under FDA regulations, activities are research when they involve:

- Use of a drug other than the use of a FDA approved drug in the course of medical practice
- Use of a medical device other than the use of a FDA approved medical device in the course of medical practice
- Gathering data that will be submitted to or held for inspection by FDA in support of a FDA marketing permit for a food, certain dietary supplements, an infant formula, a food or color additive, a drug, biologic or medical device for human use, or an electronic product.

The Common Rule and FDA definition of "human subject" differ. The Common Rule defines *human subject* as a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or
(2) identifiable private information" while the FDA defines *human subject* as an

individual who is or becomes a participant in research, either as a recipient of the test article or as a control. If the research involves a medical device, individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be either a healthy human or a patient.

Exempt Human Subjects Research

The federal Common Rule identifies six categories of human subjects research that may be eligible for exemption from IRB review. UW-Madison IRBs apply these six exemption categories only to studies determined to be no more than minimal risk and that are not FDA-regulated.

Human subjects research that qualifies as exempt under one of the federal categories must nonetheless satisfy the UW-Madison's ethical standards for the protection of human research participants.

If an investigator thinks his or her research falls into one of these exemption categories, he or she must still submit a protocol to an IRB. **Only an IRB can determine whether the human subjects research is exempt.** The IRB has the right not to exempt a protocol and to require full review by the convened IRB or expedited review by an IRB member or IRB subcommittee, particularly if the research involves a sensitive population or sensitive topic.

If a study is determined to be exempt from IRB review, it is not subject to continuing review or other rules governing human research, such as rules on informed consent. However, the HIPAA Privacy Rule applies to all exempt research that uses protected health information (PHI). HIPAA Privacy Rule requirements do not apply to exempt research using information that has been de-identified.

5. INFORMED CONSENT

Unless the IRB determines that a waiver of informed consent, or waiver of a signed informed consent document is appropriate for a study or has determined a study to be exempt, an investigator is responsible for ensuring:

- informed consent is obtained and documented using only current IRB approved consent forms, and
- the subject receives a copy of the informed consent document, and
- informed consent is obtained prior to the conduct of research procedures.

Consent documents with the IRB approval date should be used to obtain written consent from subjects. All subjects must be given a copy of the consent form. When appropriate, a copy of the consent form must be scanned into the subject's medical

record. If the research is conducted at the William S. Middleton Memorial Veteran's Hospital, additional consent and retention requirements apply.

PIs are responsible for ensuring the conduct of an adequate and appropriate consent process. When referring to "Informed Consent", it is important to differentiate between the informed consent document and the informed consent process. Obtaining informed consent is a process and not solely obtaining a signature on a form. PIs are required to ensure that the consent process is conducted and is appropriate for the research study and subject population.

PIs are responsible for ensuring the consent process is documented appropriately. Unless the IRB has granted a waiver of informed consent or a waiver of informed consent documentation, the study team should have a process in place to document the consent process and any assent process (in the case where minors or individuals with impaired decision-making capacity are enrolled) in the research files for each subject.

6. HIPAA PRIVACY RULE

All researchers who are part of the University of Wisconsin Health Care Component (HCC) or Affiliated Covered Entity (ACE) or collaborating with someone within the HCC or ACE and who are using or disclosing protected health information (PHI) must obtain written permission (i.e., an authorization) from subjects for the use of the PHI or obtain a waiver or alteration of authorization from the IRB.

7. COMPLIANCE WITH THE IRB APPROVED PROTOCOL AND APPLICATION

Research teams must adhere to the conditions of IRB approval, which includes the

information provided in the IRB application and any supporting materials such as a formal study protocol. **This means the research team cannot perform any procedures, visits, or interactions that are not in the IRB-approved protocol and they must also perform what is specified in the protocol.** Changes to the study procedures can only be made before obtaining IRB approval in cases where a change is needed to eliminate an apparent immediate hazard to subjects.

8. REQUIREMENTS AFTER IRB APPROVAL: CHANGES OF PROTOCOL

If modifications to the IRB approved materials are necessary, a change of protocol must be submitted to, and approved by, the IRB prior to implementing the change. The exception to this may occur when a change is necessary to eliminate apparent

immediate hazards to participant(s). Failure to conduct the study according to the IRB approved protocol is considered noncompliance.

To change any aspect of a research study, including revisions to an approved protocol, consent documents, HIPAA authorization forms, instruments, and recruitment methods and materials, a change of protocol must be submitted to the IRB for review and approval. Proposed changes of protocol are required to be submitted to the IRB as soon as possible and no later than 60 days after the receipt of an amendment generated by an external sponsor.

9. REQUIREMENTS AFTER IRB APPROVAL: CONTINUING REVIEW

Federal regulations require IRBs to review and approve all research protocols at intervals appropriate to the degree of risk, but not less than once per year. As a courtesy, the IRB sends email reminder notices to study teams, including PIs, prior to the expiration of approval date. However, investigators are responsible for monitoring their approval periods and submitting a *Continuing Review Protocol Progress Report* form for IRB review in a timely manner (i.e., at least 2 months prior to the expiration date). If IRB approval of a protocol expires, research activities must cease until re-approval of the protocol is obtained unless the PI demonstrates that procedures are necessary to ensure subject safety.

Closure Report: When the research is completed, investigators are expected to provide the IRB with a *Protocol Closure* report.

IN THE CASE OF FDA-REGULATED RESEARCH, THE PI IS ALSO REQUIRED TO DO THE FOLLOWING:

- **Annual Progress Reports**: The holder of the Investigational New Drug

(IND)/Investigational Device Exemption (IDE) application with the FDA (e.g. sponsor, investigator, or institution) is required to submit annual reports to the FDA within 60 days of the anniversary date that the application went into effect. This annual report should include the protocol information, the progress of the investigation, enrollment (and planned enrollment) information, a tabular summary of all adverse events, changes to the investigator's brochure, and a description of the investigational plan for the coming year.

- **Safety Report:** Investigators are required to promptly report to the IND/IDE holder (or the FDA if the investigator is the IND/IDE holder) any adverse effect that may be reasonable regarded as caused by or probably caused by the drug under investigation. If the suspected adverse reaction also meets the definitions of serious and unexpected, it must then be reported expeditiously.

- **Final Report:** Investigators are required to provide a final report shortly after completion of the investigator's participation in the investigation

REMINDER: *If the investigator or the investigator's institution holds the IND of the drug under investigation, or the IDE of the device under investigation, the investigator is required to communicate directly with the FDA.*

10. REQUIREMENTS AFTER IRB APPROVAL: UNANTICIPATED PROBLEMS

Federal regulations and institutional policies require that investigators report to the IRB any unanticipated problems that pose risks to subjects or others that are related to the research. These should be reported to the IRB in accordance with the campus unanticipated problems policy.

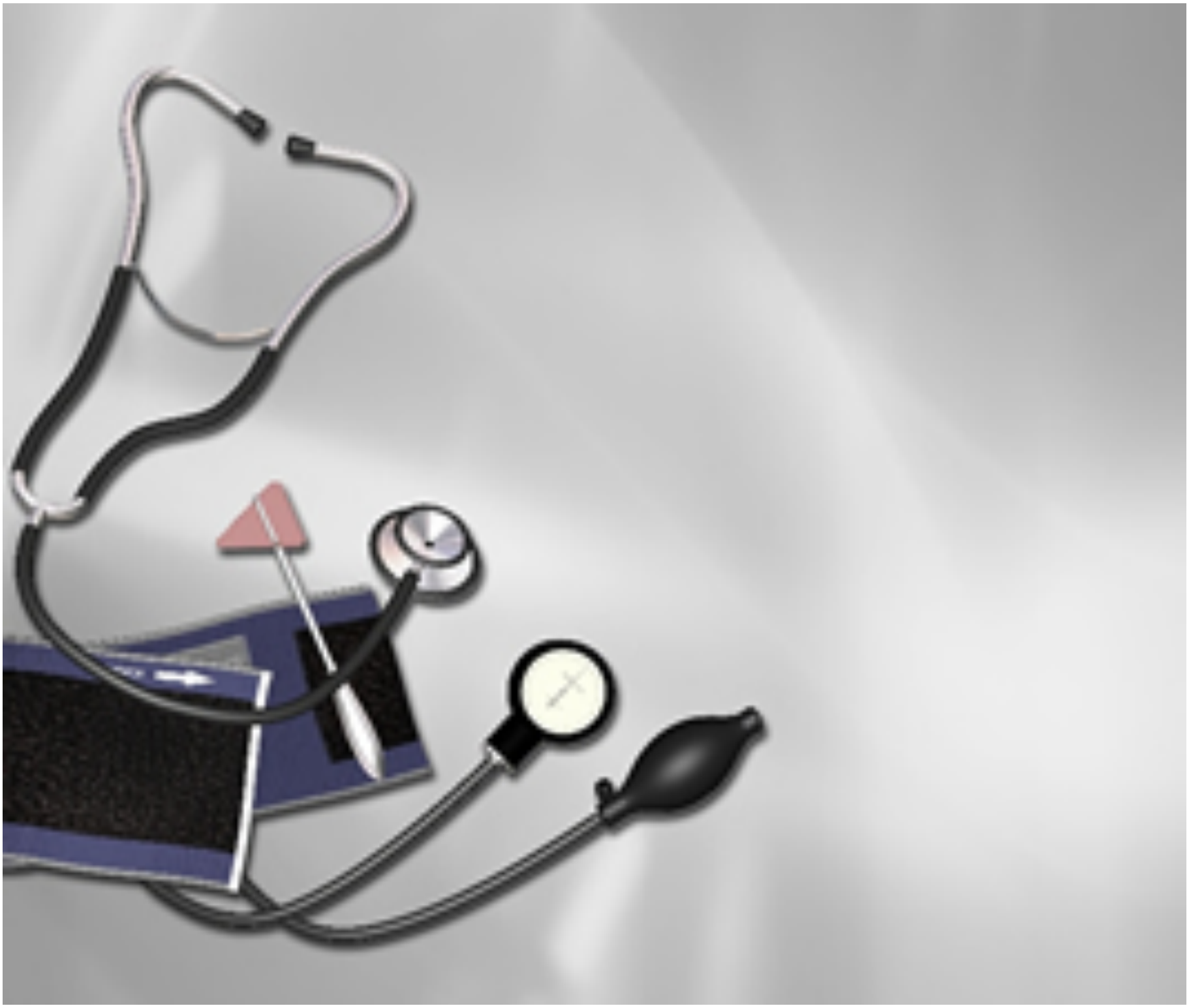
Unanticipated problem is a broad term that includes not only unfavorable outcomes that have occurred that were not expected, but also the development of potentially increased risks of harm occurring in the future. According to guidance developed by the Office for Human Research Protections (OHRP), an unanticipated problem is an incidence, experience, or outcome that meets all 3 of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

11. REQUIREMENTS AFTER IRB APPROVAL: NONCOMPLIANCE

Federal regulations and institutional policies require that investigators report noncompliance with IRB-approved documents or research regulations to the IRB. Noncompliance means any failure to follow (1) federal regulations, VA guidance, state laws or institutional policies relevant to human subjects research, or (2) the requirements and determinations of the reviewing IRB.

12. ADEQUATE MEDICAL OVERSIGHT



For clinical research studies involving drugs, devices, biologics, or a significant physical intervention, a qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the study, should be responsible for all study-related medical (or dental) decisions.

This responsibility includes:

- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable or when specialized care is needed)
- Adhering to the protocol so that study subjects are not exposed to unreasonable risks
- Informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed.

13. RECORD KEEPING AND RECORD RETENTION

State and federal regulations require study teams to maintain complete and accurate study records. Study records should be stored in a secure manner to protect the privacy of subjects and to reduce the risk of damage. Any or all of the study related documents may be subject to, and should be available for, audit or inspection by a regulatory authority. Study records can be archived after completion, but must be maintained for a specified amount of time depending on the requirements of the funding agency, sponsor, FDA or entity providing oversight. There may be other requirements that researchers must look into before disposing of research records; for example, the institution recommends maintaining records for at least seven years to dispute any allegations of research misconduct.

14. DISPOSITION OF DRUGS, BIOLOGICS AND DEVICES

When research involves administration of drugs, biologics, or devices to subjects, PIs are responsible for maintaining adequate records regarding the receipt, use and disposition of investigational drugs or devices used in a research study. Records include date and quantity dispensed and/or used by the subject, the investigational product return and final disposition. The study team is required to provide a plan to the IRB for control of any investigational drugs, biologics, or devices used in a research study.

15. CLINICALTRIALS.GOV REGISTRATION AND RESULTS REPORTING

Many clinical research studies involving human subjects must be registered on and have results posted to ClinicalTrials.gov as mandated by the Food and Drug Administration (FDA) and/or International Committee of Medical Journal Editors (ICMJE).

The FDA requires study registration along with results and adverse event reporting for all phase II - IV interventional drug, biologic or device trials ("applicable clinical trials") within 21 days of the first subject's enrollment. Failing to register "applicable clinical trials" in a timely manner can result in significant monetary penalties. The ICMJE requires registration of any interventional health outcome studies – including Phase I trials – prior to subject enrollment. The ICMJE does not currently require results reporting. Failing to register trials covered by the ICMJE requirements in a timely manner can result in the rejection of publications based on the failure to register the trial.

Refer to the **Support for Clinical Trials Registration & Results Reporting** webpage for current UW policies and requirements.

16. ADDITIONAL RESPONSIBILITIES FOR MULTI-SITE RESEARCH

When IRB review of a study is deferred to a non-UW IRB, the PI and study team must still comply with relevant UW-Madison requirements and must also be familiar with the requirements of the IRB of record, which may differ from that required by the UW. These responsibilities include complying with the requirements of the reviewing IRB in addition to those of the PI's own institution and ensuring all institutional requirements are met, in addition to the PI's own institution (e.g., required approvals or sign-offs from ancillary committees).

When the UW serves as the coordinating center for a study, some of the additional requirements that the PI and study team are responsible for include ensuring IRB approvals from all sites are in place before human subjects research occurs at those sites and promptly communicating changes of protocol, new information, and unanticipated problems to all study sites and ensuring that any changes are implemented.

Refer to the **UW-Madison and Federal Website Links** webpage and the **Clinical Research Toolkit** for templates and tools for clinical researchers.

Take the quiz for Investigator Responsibilities - Biomedical

View Post-Course Completion Options
