GOOD CLINICAL PRACTICE GUIDEBOOK

CARE CLINICAL RESEARCH CORP.

GOOD CLINICAL PRACTICE (GCP)

WHAT IS GOOD CLINICAL PRACTICE AND WHY IS IT NECESSARY FOR CLINICAL RESEARCH?

150+ PAGES OF EVERYTHING YOU NEED TO KNOW ABOUT GCP!

GOOD CLINICAL PRACTICE GUIDEBOOK

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GOOD CLINICAL PRACTICE GUIDEBOOK

Introduction to Good Clinical Practice (GCP)

Chapter One

Good Clinical Practice (GCP) is a set of international ethical and scientific quality standards that govern the design, conduct, recording, and reporting of clinical trials involving human subjects. GCP guidelines ensure that clinical trials are conducted with the highest level of safety, efficacy, and data integrity.

The **International Conference on Harmonization (ICH)** developed the current GCP guidelines, which are accepted by regulatory authorities in the United States, Europe, Japan, and other countries. The guidelines define the responsibilities of the sponsor, investigator, and **institutional review board (IRB)** or **ethics committee (EC)** in the conduct of a clinical trial.

The key principles of GCP include:

1. Protection of human subjects: Clinical trials must be conducted in a way that protects the safety, rights, and well-being of human subjects.
2. Informed consent: Informed consent must be obtained from all participants before they participate in the study.
3. Ethics committee review: The study must be reviewed and approved by an independent IRB or EC before it can begin.
4. Study design and conduct: The study must be scientifically sound and conducted according to a detailed protocol that outlines the study objectives, study population, study procedures, and data analysis plan.
5. Data quality and integrity: The data collected during the study must be accurate, complete, and verifiable.
6. Recordkeeping and documentation: Records of the study, including study data and documents, must be kept in a way that allows for complete and accurate reporting of the study results.
7. Monitoring: The study must be monitored to ensure that it is being conducted according to the protocol and GCP guidelines.
8. Investigator responsibilities: The investigator is responsible for conducting the study according to the protocol, ensuring the safety and welfare of study participants, and reporting adverse events to the sponsor and IRB or EC.
9. Sponsor responsibilities: The sponsor is responsible for designing the study, providing the study drug or device, ensuring that the study is conducted

according to the protocol and GCP guidelines, and analyzing and reporting the study results.

Overall, GCP is designed to ensure that clinical trials are conducted in a way that is ethical, scientifically sound, and protects the safety and well-being of study participants. Adherence to GCP guidelines is essential for the conduct of high-quality clinical trials that are accepted by regulatory authorities around the world.

GCP Guidelines

GCP Guidelines

The Good Clinical Practice (GCP) guidelines are a set of international ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials that involve human participants. These guidelines were developed in collaboration with the International Council for Harmonization (ICH), a global organization that aims to standardize the requirements for the development and registration of pharmaceutical products.

The GCP guidelines provide a framework to ensure the protection of the rights, safety, and confidentiality of human subjects in clinical trials, and to ensure the accuracy and credibility of the data generated from the trials. The guidelines cover all aspects of clinical trials, including trial design, ethics, data collection, monitoring, analysis, and reporting.

The principles outlined in the GCP guidelines can be applied to all types of clinical investigations, including those involving investigational products, marketed drugs, medical devices, or behavioral interventions. The guidelines are recognized and followed by regulatory authorities and research organizations worldwide to ensure that clinical trials are conducted in a consistent and ethical manner, and that the results obtained are reliable and trustworthy.

ICH GCP Principles

The ICH GCP guidelines describe the ethical and scientific principles that should be followed when designing, conducting, recording, and reporting clinical trials involving human participants. The principles include the following:

1. Clinical trials should be conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki and the applicable regulatory

requirements.

2. The rights, safety, and well-being of trial participants should take precedence over the interests of science and society.

3. The clinical trial should be scientifically sound and described in a clear, detailed, and well-structured protocol.

4. The trial should be conducted by qualified individuals who have received the necessary training, and who are aware of and comply with GCP guidelines.

5. The informed consent of trial participants should be obtained before they participate in the trial.

6. The trial should be monitored to ensure compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

7. The data generated from the trial should be accurate, complete, and verifiable.

8. The confidentiality and privacy of trial participants should be protected.

9. Investigational products should be developed, manufactured, and tested in accordance with the applicable regulatory requirements.

10. The results of the trial should be reported accurately and completely, and in a timely manner.

These principles are intended to ensure that clinical trials are conducted in a manner that protects the rights and welfare of participants, generates reliable and trustworthy data, and meets the applicable regulatory requirements.

ICH Guideline E6

The **ICH E6 guideline** for Good Clinical Practice (GCP) is a set of internationally recognized guidelines for the design, conduct, monitoring, recording, auditing, analysis, and reporting of clinical trials. The guideline provides a standardized framework for the ethical and scientific principles that should be followed during the conduct of clinical trials involving human subjects.

The ICH E6 guideline outlines the essential elements of a clinical trial protocol, including the study objectives, study design, eligibility criteria, treatment plan, and statistical analysis plan. The guideline also specifies the responsibilities of the sponsor, investigator, and monitor in conducting the clinical trial.

Additionally, the guideline sets out requirements for the collection and handling of trial data, including the documentation of the informed consent process, adverse event reporting, and record retention. It also outlines procedures for ensuring the quality of the trial data, such as monitoring visits and audits.

The ICH E6 guideline emphasizes the importance of human subject protection and the ethical conduct of clinical trials. It requires that the study is designed to minimize risk to participants and that their welfare is given the highest priority. It also requires that participants are fully informed about the trial, the risks, and benefits, and have given informed consent before participating.

Overall, the ICH E6 guideline for GCP documentation provides a comprehensive set of requirements and recommendations to ensure the safety, quality, and reliability of clinical trial data, thereby protecting the rights and welfare of trial participants and maintaining public trust in the integrity of clinical research.

Code of Federal Regulations

What is the Code of Federal Regulations?

The **Code of Federal Regulations (CFR)** is a collection of rules, regulations, and directives issued by federal executive branch agencies and departments of the United States government. The CFR is organized into 50 titles that cover a wide range of topics, including agriculture, commerce, energy, environmental protection, health and human services, immigration, labor, transportation, and many others.

The CFR is designed to provide a comprehensive and systematic presentation of federal regulations that have general applicability and legal effect. It includes the full text of federal regulations, as well as explanations and guidance on how to interpret and apply the regulations. The CFR is updated annually to reflect changes in the federal regulatory landscape, and it is widely used by government officials, lawyers, researchers, and others to understand and comply with federal regulations.

The CFR is published by the Office of the Federal Register, which is an agency of the National Archives and Records Administration (NARA). The Office of the Federal Register is responsible for publishing, maintaining, and authenticating the official text of federal regulations, as well as other official documents and publications of the federal government.

Regulations to be Familiar with

The sections of the CFR that are directly relevant to research involving human participants are found in **Title 45 (Public Welfare), specifically in Part 46, Protection of Human Subjects**. Part 46 is also commonly referred to as the "**Common Rule**," which is a set of regulations that applies to federally-funded research involving human subjects.

Part 46 outlines the basic ethical principles and regulatory requirements for the protection of human subjects in research. It defines the criteria for the Institutional Review Board (IRB) approval of research involving human subjects and establishes the requirements for obtaining informed consent from research participants.

Part 46 also sets out the requirements for the reporting of unanticipated problems and adverse events in research involving human subjects. Additionally, it specifies the procedures for the suspension or termination of research involving human subjects and outlines the responsibilities of investigators, institutions, and IRBs in ensuring compliance with the regulations.

Other sections of the CFR that are relevant to research involving human participants include **Title 21 (Food and Drugs) and Title 42 (Public Health)**, which contain regulations related to the use of investigational drugs and devices in research, as well as regulations related to the protection of human subjects in research conducted or supported by the Department of Health and Human Services.

Here are sections you should be familiar with:

- **21 CFR 11**: Electronic Records; Electronic Signatures - This regulation establishes the requirements for the use of electronic records and electronic signatures in FDA-regulated activities.

- **21 CFR 50**: Protection of Human Subjects - This regulation outlines the basic ethical principles and regulatory requirements for the protection of human

subjects in research, including the requirements for informed consent.

- **21 CFR 54**: Financial Disclosure by Clinical Investigators - This regulation requires that clinical investigators disclose certain financial interests that could affect the objectivity of clinical research.

- **21 CFR 56**: Institutional Review Boards - This regulation sets out the criteria for the Institutional Review Board (IRB) approval of research involving human subjects, as well as the responsibilities of the IRB in ensuring compliance with the regulations.

- **21 CFR 312**: Investigational New Drug Application - This regulation establishes the requirements for the submission of an Investigational New Drug (IND) application to the FDA, which is required before conducting clinical trials of a new drug in humans.

- **21 CFR 314**: Applications for FDA Approval to Market a New Drug - This regulation outlines the requirements for the submission of a New Drug Application (NDA) to the FDA, which is required before a new drug can be marketed in the United States.

- **42 CFR 2 and 42 CFR 2a**: Confidentiality of Substance Use Disorder Patient Records - These regulations establish the privacy protections for substance use disorder patient records and set out the circumstances under which patient records can be disclosed.

- **45 CFR 46**: Protection of Human Subjects - This regulation, also known as the Common Rule, outlines the basic ethical principles and regulatory requirements for the protection of human subjects in research, including the requirements for informed consent and the criteria for IRB approval.

- **45 CFR 160 and 45 CFR 164**: Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules - These regulations establish the privacy and security requirements for protected health information (PHI) under HIPAA, including the requirements for obtaining patient authorization for the use and disclosure of PHI.

The FDA is responsible for protecting public health by regulating human drugs and biological products, animal drugs, medical devices, tobacco products, food (including animal food), cosmetics, and electronic products that emit radiation.

Research that involves controlled substances must comply with U.S. Drug Enforcement Administration (DEA) regulations, which are outlined in 21 CFR 1300.

Scientific investigations involving drugs are subject to FDA regulations. In addition to the regulations for Investigational New Drugs (21 CFR 312) and marketing of drugs (21 CFR 314) mentioned in Part 3 of this module, FDA regulations also apply to Good Manufacturing Practice (GMP) requirements for drugs. These requirements are outlined in 21 CFR 210 - Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs, and 21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals. These regulations establish requirements for the manufacturing, processing, packing, and holding of drugs to ensure that they meet quality standards and are safe for human use.

The HIPAA Privacy Rule and Security Rule are federal laws that safeguard the privacy of research participants and their personal health information. We will go in depth about HIPAA in the privacy and safety module.

NIH policies regulate grant management.

Various entities such as countries, states, cities, and institutions may establish their own policies to safeguard human participants involved in research. These policies may have stricter requirements than those mandated by federal regulations. Researchers must ensure that their studies are designed and executed in a way that conforms with both federal and local policies on human participant protection, particularly if local policies are more stringent.

Chapter One Resources

Summary of Key Points:

- Good Clinical Practice (GCP) is an ethical and scientific standard for conducting clinical trials that encompasses all aspects of the process from design to reporting.
- GCP ensures that trial participants are protected, and the data and reported results are accurate and credible.
- GCP guidelines have evolved in response to past incidents of research participant abuse, and all research studies involving human participants should adhere to its guidelines, with all research staff receiving appropriate training.
- To receive funding for projects involving human research participants, all key personnel must undergo training in the protection of human research participants.
- The principles of GCP are codified in several sections of the Code of Federal Regulations (CFR).
- Noncompliance with GCP regulations can lead to fines, penalties, or the suspension of a research study.
- Additional policies for human participant protection may be implemented at various levels, including countries, states, cities, and institutions.
- Researchers must ensure that their studies comply with both local and federal requirements, even if local policies are more stringent than federal regulations.

What are Institutional Review Boards (IRB)?

Chapter Two

Institutional Review Boards

What is an Institutional Review Board?

An **Institutional Review Board (IRB)** is a committee established by an institution or organization that conducts research involving human participants. The primary responsibility of an IRB is to ensure the protection of the rights, welfare, and safety of human participants in research. IRBs are responsible for reviewing and approving research protocols, monitoring the progress of ongoing studies, and ensuring that researchers comply with ethical and regulatory standards, including informed consent and confidentiality. IRBs are typically composed of diverse members, including scientists, non-scientists, and community representatives, who have expertise in areas such as medicine, ethics, law, and social sciences.

What does an IRB do?

An Institutional Review Board (IRB) is responsible for ensuring the protection of human participants involved in research. Specifically, the IRB has the following duties:

1. Review research protocols: The IRB must review research protocols to ensure that the study is designed in a manner that minimizes risks to human participants and that the benefits of the research justify any potential harm.

2. Monitor the progress of ongoing studies: The IRB must monitor the progress of ongoing studies to ensure that the researchers continue to comply with ethical and regulatory standards.

3. Ensure informed consent: The IRB must ensure that participants in research studies have been fully informed about the study, including the risks and benefits, and that they have given their voluntary, informed consent to participate.

4. Protect participant confidentiality: The IRB must ensure that participant confidentiality is protected and that their privacy is maintained.

5. Ensure the selection of participants is fair: The IRB must ensure that the selection of participants is fair and does not discriminate on the basis of race,

gender, age, or other factors.

6. Determine if there are any conflicts of interest: The IRB must determine if there are any conflicts of interest that may affect the study or the protection of participants.

Overall, the IRB plays a critical role in ensuring that research involving human participants is conducted ethically and in compliance with all applicable regulations and guidelines.

An IRB may suspend or terminate ongoing research if it determines that the study poses an unacceptable risk to human subjects or if the study is not being conducted in compliance with ethical and regulatory requirements.

Here are some specific reasons why an IRB may suspend or terminate ongoing research:

1. Noncompliance with ethical or regulatory requirements: If the IRB determines that the study is not being conducted in compliance with ethical and regulatory requirements, it may suspend or terminate the study. For example, if the study is not obtaining informed consent from participants, if the study is exposing participants to unnecessary risks, or if the study is not properly monitoring adverse events, the IRB may decide to suspend or terminate the study.

2. Unacceptable risks to human subjects: If the IRB determines that the risks to human subjects are unacceptable or that the potential benefits of the research do not outweigh the risks, it may suspend or terminate the study. For example, if the study is exposing participants to significant physical or psychological harm, or if the study is not adequately protecting the privacy and confidentiality of participants, the IRB may decide to suspend or terminate the study.

3. Emergence of new safety concerns: If new safety concerns arise during the course of the study, the IRB may decide to suspend or terminate the study. For example, if unexpected adverse events occur that were not previously identified, the IRB may need to re-evaluate the risks and benefits of the study and decide whether to suspend or terminate the study.

Overall, the IRB's responsibility is to ensure that ongoing research is conducted in a manner that protects the rights and welfare of human subjects. If the IRB determines that there are ethical or regulatory concerns, or if the risks to human subjects are unacceptable, it may decide to suspend or terminate the study to protect the safety and well-being of the participants.

Members of an IRB

The composition of an Institutional Review Board (IRB) is specified in federal regulations, specifically 45 CFR 46, which outlines the requirements for the protection of human research participants. The regulations require that an IRB be composed of at least five members with varying backgrounds and expertise.

Here are the typical members of an IRB:

1. Chairperson: The Chairperson is responsible for leading the IRB and ensuring that the IRB operates in accordance with federal regulations and ethical standards. The Chairperson must have a good understanding of research ethics, federal regulations, and the research process.

2. Scientist: At least one member of the IRB must have expertise in the scientific area relevant to the research studies being reviewed. This member is responsible for evaluating the scientific merit of the research proposals and ensuring that the study design is appropriate.

3. Non-scientist: At least one member of the IRB must have no scientific background and represents the community's views. This member serves as a layperson representative who can provide a perspective that is not influenced by scientific or medical expertise.

4. Ethicist: At least one member of the IRB must be an expert in research ethics. This member is responsible for ensuring that the research studies are conducted in an ethical and responsible manner, and that the rights and welfare of research participants are protected.

5. Additional members: IRBs may have additional members with various backgrounds, including clinical researchers, statisticians, attorneys, and patient advocates. The number and types of additional members may vary based on the types of research studies being reviewed.

Overall, the IRB's membership is intended to provide a diverse set of perspectives and expertise to ensure that research studies are reviewed and approved in an ethical and responsible manner. The IRB's responsibility is to ensure that research studies are conducted in accordance with ethical principles, regulatory requirements, and the rights and welfare of research participants are protected.

Conflicts of interest can be a significant concern for IRB members as they can potentially compromise the objectivity and impartiality of the review process. To address this issue, IRBs are required to have policies in place for identifying and managing conflicts of interest among its members.

Specifically, IRB members must disclose any financial or other interests that could potentially create a conflict of interest with the research studies under review. If a member has a significant financial or other interest in a research study, they may be required to recuse themselves from the review process to avoid any potential conflicts of interest.

Non-voting members may also be part of an IRB, and they typically serve in an advisory capacity. These members may include representatives from the institution's legal counsel, research administration, or other departments that can provide additional expertise or support to the IRB. Non-voting members are not involved in the decision-making process of the IRB, but they may participate in discussions and provide feedback or recommendations to the voting members.

Overall, conflicts of interest and the inclusion of non-voting members are important considerations for IRBs to ensure that the review process is fair, objective, and transparent. The ultimate goal of an IRB is to protect the rights and welfare of research participants, and these measures help to ensure that this goal is met.

IRB Responsibilities

An Institutional Review Board (IRB) has several primary responsibilities to ensure that research studies involving human participants are conducted ethically, legally, and in a manner that protects the rights and welfare of the participants. Here are some of the key responsibilities of an IRB:

1. Review research proposals: The primary responsibility of an IRB is to review and approve or disapprove research proposals that involve human participants. This includes reviewing the study design, methodology, risks and benefits to

participants, and the informed consent process.

2. Monitor ongoing studies: The IRB is responsible for monitoring the progress of ongoing studies to ensure that they continue to meet ethical and regulatory standards. This includes reviewing any modifications to the study design or protocol and ensuring that any adverse events are reported and addressed appropriately.

3. Educate researchers and participants: The IRB provides education and guidance to researchers and participants about ethical and legal requirements related to human research. This includes educating researchers about the informed consent process, the importance of protecting participant confidentiality, and the need to report adverse events.

4. Maintain records: The IRB is responsible for maintaining accurate and complete records related to the review and approval of research studies. This includes all documentation related to the review process, including meeting minutes, research proposals, and any communication with researchers.

5. Ensure compliance with regulations: The IRB is responsible for ensuring that all research studies involving human participants are conducted in compliance with federal regulations and guidelines. This includes adhering to the principles of the Belmont Report, which includes respect for persons, beneficence, and justice.

6. Review and address any concerns or complaints: The IRB is responsible for reviewing and addressing any concerns or complaints related to research studies involving human participants. This includes responding to any allegations of research misconduct or ethical violations.

Overall, the IRB plays a critical role in ensuring that research studies involving human participants are conducted in a manner that protects their rights and welfare. The IRB's responsibilities involve reviewing research proposals, monitoring ongoing studies, educating researchers and participants, maintaining accurate records, ensuring compliance with regulations, and addressing any concerns or complaints.

Criteria for IRB Approval of Research (The Belmont Report)

What is the Belmont Report?

The Belmont Report is a seminal document that outlines ethical principles and guidelines for research involving human subjects. It was published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, in response to growing concerns about unethical research practices.

The Belmont Report is named after the Belmont Conference Center, where the Commission met to discuss and develop the report. The report is based on three core ethical principles: respect for persons, beneficence, and justice.

Respect for persons refers to the idea that individuals have the right to make informed decisions about their participation in research, and that researchers should obtain informed consent from their subjects. Beneficence refers to the obligation of researchers to maximize benefits and minimize harms to their subjects. Justice refers to the fair distribution of the benefits and burdens of research.

The Belmont Report also outlines several guidelines for ethical research, including the requirement for informed consent, the need for risk-benefit analysis, and the obligation to protect the privacy and confidentiality of research subjects.

Overall, the Belmont Report has been instrumental in establishing ethical standards for research involving human subjects and has been widely influential in shaping research ethics guidelines in the United States and around the world.

Criteria for IRB Approval of Research

Criteria 1: Risks to Participants are Minimized - This criterion requires researchers to minimize the potential risks to participants as much as possible. Researchers must identify and assess all potential risks to participants, including physical, psychological, social, and economic risks. They must then take steps to minimize these risks, such as modifying the study procedures, providing safety equipment, or monitoring participants for adverse effects.

Criteria 2: Risks to Participants are Reasonable in Relation to Anticipated Benefits - This criterion requires that the risks to participants be reasonable in relation to the anticipated benefits of the study. Researchers must weigh the potential benefits of the study against the potential risks to participants, and ensure that the benefits justify the risks.

Criteria 3: Selection of Participants is Equitable - This criterion requires researchers to ensure that the selection of participants is fair and equitable, and does not discriminate against any particular group. Researchers must take steps to avoid selecting participants based on factors such as race, gender, age, or socioeconomic status, and must ensure that the selection process is unbiased.

Criteria 4: Informed Consent is Properly Obtained and Documented - This criterion requires researchers to obtain informed consent from participants, and to document the consent process. Informed consent means that participants are fully informed about the study, including its purpose, procedures, risks, and benefits, and that they voluntarily consent to participate. Researchers must provide participants with written information about the study, answer any questions they may have, and obtain their signature on a consent form.

Criteria 5: Adequate Provision is Made to Protect Participants' Privacy and Maintain the Confidentiality of Data - This criterion requires researchers to take steps to protect the privacy and confidentiality of participants and their data. Researchers must ensure that any identifying information about participants is kept confidential and that data is stored securely. They must also obtain participants' consent for the use and disclosure of their data.

Criteria 6: Additional Safeguards are Included for Vulnerable Populations - The final criteria for IRB approval of research is that additional safeguards are included for vulnerable populations. This includes groups such as children, pregnant women, prisoners, and individuals with cognitive or mental disabilities. Researchers must take extra precautions to protect these populations, including obtaining additional consent from a legal guardian or ensuring that the participant fully understands the risks and benefits of the study.

Expedited Review

An IRB (Institutional Review Board) may use an expedited review procedure for research studies that involve minimal risk to participants. The expedited review process allows the IRB to review and approve the study without convening a full board meeting.

According to the U.S. Department of Health and Human Services regulations for the protection of human subjects, expedited review may be used for research that involves:

1. Collection of blood samples or other bodily fluids by noninvasive means
2. Collection of data through noninvasive procedures (e.g., surveys, questionnaires, or observation of public behavior)
3. Research on individual or group behavior or characteristics, such as studies of perception, cognition, or personality
4. Research involving the use of existing data or specimens, if these are publicly available or if the information has been de-identified
5. Certain types of research on drugs or medical devices for which an investigational new drug application (IND) or investigational device exemption (IDE) is not required.

To qualify for expedited review, the study must meet all of the following criteria:

1. The research involves no more than minimal risk to participants;
2. The research involves procedures that are already being performed for diagnostic or treatment purposes;
3. The research involves collection of data or specimens that are noninvasive; and
4. The research does not involve sensitive or potentially stigmatizing topics.

If the study meets these criteria, then the IRB may use the expedited review procedure to approve the study. This process typically involves a review by one or more IRB members, rather than the entire board, and can be completed more quickly than a full board review.

Investigators' Responsibilities to the IRB

Investigators who conduct research with human subjects have several important responsibilities to the IRB (Institutional Review Board) overseeing their study. These responsibilities include:

1. Submitting a complete and accurate protocol: Investigators are responsible for submitting a detailed and accurate protocol to the IRB that describes the study design, methods, and procedures. The protocol should also describe how the

investigator will minimize risks to participants and ensure their welfare is protected.

2. Obtaining informed consent: Investigators must obtain informed consent from participants before enrolling them in the study. This means providing potential participants with all necessary information about the study and its risks and benefits, and ensuring that they understand the information before agreeing to participate. Investigators must also document the informed consent process in a written consent form or other appropriate means.
3. Reporting adverse events: Investigators must report any adverse events or unanticipated problems that occur during the study to the IRB in a timely manner. These events can include unexpected side effects from study interventions, participant withdrawals, or protocol deviations.
4. Adhering to the approved protocol: Investigators must conduct the study according to the protocol that has been approved by the IRB. Any changes to the study design or procedures must be reviewed and approved by the IRB before they are implemented.
5. Maintaining accurate records: Investigators must maintain accurate and complete records of the study, including all participant data and documentation of informed consent. These records must be kept confidential and secure.
6. Cooperating with IRB requests: Investigators must cooperate with any requests from the IRB for additional information or documentation related to the study. They must also comply with any decisions made by the IRB regarding the study design or conduct.

Failure to comply with these responsibilities can result in serious consequences, including suspension or termination of the study, loss of funding, or disciplinary action against the investigator. Therefore, it is important for investigators to work closely with the IRB and take their responsibilities seriously in order to ensure the safety and welfare of participants.

Overall, investigators have a responsibility to conduct research in an ethical and responsible manner, while ensuring the safety and well-being of study participants. The IRB plays a critical role in this process by providing oversight and guidance to investigators throughout the study.

IRB and Multi-Site Research

NIH-funded multi-site trials involve numerous institutions and study sites that collaborate on a single research study. Each institution is responsible for ensuring the safety and rights of research participants at their respective sites. However, with the NIH's policy on

using a single institutional review board (sIRB) for multi-site research starting from May 25, 2017, multi-institutional research involving non-exempt human participants in the US will use a single IRB to streamline the review process while maintaining participant protection. This policy is based on 45 CFR 46.114 and aims to enhance efficiency and reduce administrative burden. Additional information and resources on the use of sIRBs are available on the NIH Office of Science Policy's website.

The NIH policy on the Use of a Single Institutional Review Board (sIRB) for Multi-Site Research was implemented to streamline the IRB review process for multi-site trials involving human subjects. This policy applies to all NIH-funded studies that involve non-exempt human subjects research at more than one institution.

Under this policy, a single IRB is designated to provide review and oversight for all study sites, rather than each site having its own IRB. The single IRB is responsible for ensuring that the study is conducted in accordance with ethical principles, federal regulations, and institutional policies. This policy is intended to reduce administrative burden and increase efficiency in the IRB review process, while maintaining protections for human study participants.

However, there are some exceptions to the use of a single IRB. For example, some studies may require additional local review due to local regulations, cultural considerations, or unique populations. In these cases, the single IRB may work with local IRBs to ensure that all ethical and regulatory requirements are met.

It is important to note that while the single IRB is responsible for overseeing the study, each participating institution is still responsible for ensuring that the rights and welfare of research participants are protected at their respective sites. This includes obtaining local regulatory approvals, recruiting participants, obtaining informed consent, and collecting and managing data.

Overall, the use of a single IRB for multi-site research can increase efficiencies and streamline the IRB review process, while maintaining protections for human study participants. Additional resources and guidance on the use of a single IRB are available from the NIH Office of Extramural Research and the NIH Office of Science Policy.

Chapter Two Resources

Summary of Key Points:

- The main function of an Institutional Review Board (IRB) is to protect the rights, safety, and well-being of human research participants.

- Federal regulations require that any study involving human participants funded by the government or involving a product regulated by the FDA must be reviewed and approved by an IRB.
- The IRB has the authority to approve or disapprove all research activities within its jurisdiction and may request modifications or even suspend previously approved studies.
- Ongoing research must be reviewed annually by an IRB to ensure that approval should be continued.
- Institutions participating in clinical studies must identify all IRBs with jurisdiction to review and approve the protocol.
- To approve a research protocol, the IRB must ensure that risks to participants are minimized and reasonable in relation to benefits, participant selection is fair, informed consent is appropriately obtained and documented, monitoring is in place to ensure safety, confidentiality is maintained, and vulnerable populations receive additional safeguards.

The Importance of Informed Consent

Chapter Three

What is Informed Consent?

Informed consent is a process by which individuals are fully informed about a research study before deciding whether or not to participate. The purpose of informed consent is to ensure that participants have a clear understanding of the nature of the research, the potential risks and benefits, and their rights as participants. Informed consent typically involves providing participants with a written document that outlines the study's purpose, procedures, risks, and benefits. Participants are also given the opportunity to ask questions and have them answered by the research team. Only after they have been fully informed and have given their voluntary and informed consent will participants be allowed to take part in the study. Informed consent is a critical component of ethical research, and it is required by law in most countries.

The process of informed consent starts with the initial contact between a potential participant and the research team. The research team explains the study's purpose, procedures, risks, and benefits to the participant in language that they can understand. The research team will then provide a written informed consent document that outlines the study's details, including any potential risks, benefits, or compensation.

If the participant agrees to participate, they will sign the informed consent document. The participant's signature on the document signifies that they have read the document, understand it, and voluntarily agree to participate. The informed consent process is an ongoing process throughout the study. If any significant changes occur to the study protocol, participants will be informed of the changes and asked to re-consent.

Participants have the right to withdraw from the study at any time without penalty or prejudice. They can withdraw their consent by notifying the research team that they no longer wish to participate.

Certain groups of people may be exempt from requiring informed consent, such as individuals who are unconscious or mentally incapacitated. In these cases, an authorized representative (such as a family member or legal guardian) may provide consent on the individual's behalf.

An informed consent document typically includes several key components, such as:

- A statement indicating that participation in the study is voluntary

- A clear explanation of the study's purpose, procedures, risks, and benefits
- A description of the participant's rights, including the right to withdraw from the study
- Information about confidentiality and data protection
- A statement indicating that the participant's data may be used for research purposes
- Contact information for the research team and the institutional review board overseeing the study.

Overall, the informed consent process is a critical component of ethical research. It ensures that participants have a clear understanding of the study's purpose and procedures and can make an informed decision about whether or not to participate.

The Informed Consent Document

According to 45 CFR 46.116, 21 CFR 50.20, and ICH E6 GCP 4.8.10, the following information should be included in an informed consent document:

1. A statement that the study involves research and an explanation of the purpose of the research.
2. A description of the expected duration of the participant's participation, including the number of visits and procedures.
3. A description of the procedures to be followed, including any experimental procedures.
4. Identification of any procedures that are experimental.
5. A description of the risks or discomforts that the participant may experience as a result of participating in the study.
6. A description of the benefits that the participant may expect from participating in the study.
7. Disclosure of alternative procedures or courses of treatment that might be available to the participant, and their important potential benefits and risks.
8. A statement that participation is voluntary, and the participant may refuse to participate or withdraw at any time without penalty or loss of benefits to which the participant is otherwise entitled.
9. An explanation of any compensation or medical treatments available if injury occurs as a result of participation in the study.
10. An explanation of whom to contact for answers to questions about the study, study-related injuries, or complaints about the study.
11. A statement of the extent to which confidentiality of records identifying the participant will be maintained.

12. For research involving more than minimal risk, an explanation of whether any compensation or medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.
13. A statement describing any costs to the participant that may result from participation in the study and whether reimbursement or compensation is available.
14. An explanation of whether any significant new findings relating to the study that may affect the participant's willingness to continue participation will be provided to the participant.

An informed consent document is an essential component of the informed consent process and typically includes several key components. These components are designed to ensure that potential research participants have all the necessary information to make an informed decision about whether or not to participate in a study.

1. Study Purpose: This section provides an overview of the study's overall purpose, including its goals, objectives, and research questions. It outlines what researchers hope to achieve by conducting the study.
2. Study Treatment and Randomization: This section explains the treatment options available to participants, including the randomization process, if applicable. It also explains the likelihood of receiving a specific treatment and the possible consequences of randomization.
3. Study Procedures: This section outlines the specific procedures involved in the study, including any tests, measurements, or interventions that participants will undergo during the study.
4. Risks of Taking Part in the Study: This section provides a detailed explanation of the potential risks associated with participation in the study. This may include physical, psychological, social, or financial risks.
5. Benefits of Taking Part in the Study: This section outlines the potential benefits of participation, both for the individual participant and for society as a whole.
6. Alternatives to Taking Part in the Study: This section describes any alternative treatments or interventions that may be available to participants, as well as their potential risks and benefits.
7. Costs of Participation and Compensation in the Event of Injury: This section outlines any costs associated with participation in the study, as well as any compensation that may be available to participants in the event of an injury.
8. Payment for Taking Part in the Study: This section describes any payment that may be available to participants for their time and effort in taking part in the study.
9. Voluntary Nature of Study: This section emphasizes that participation in the study is entirely voluntary, and participants are free to withdraw from the study at any time without penalty.

10. Confidentiality of Personal Information: This section describes how the researchers will protect the confidentiality of participants' personal information, including any data that may be collected during the study.
11. New Information that may Affect Study Participation: This section explains that participants will be informed of any new information that may affect their decision to continue participating in the study.
12. Study Contacts: This section provides the names and contact information for the researchers responsible for the study, as well as any other individuals or organizations involved in the study.
13. Duration of Participation and Number of People Taking Part in the Study: This section provides an estimate of how long participation in the study is likely to last, as well as an estimate of the total number of people who will be taking part in the study.

Special Requirements Concerning Consent

Pregnant Women

The involvement of pregnant women in clinical trials raises ethical considerations because of the potential risks to the developing fetus. The U.S. Department of Health and Human Services has established special requirements concerning the consent of pregnant women.

According to 45 CFR 46 Subpart B, pregnant women may only participate in research if all of the following criteria are met:

- The risk to the fetus is minimal;
- The purpose of the study is to obtain important data that cannot be obtained by other means;
- The research holds out the prospect of direct benefit to the pregnant woman or the fetus, or both; or the research is intended to develop important medical knowledge that will benefit the health of the pregnant woman or the fetus, or both; and
- The pregnant woman is fully informed regarding the reasonably foreseeable impact of the research on the fetus and makes an informed decision to participate.

The father may need to be present or involved in the informed consent process if he is legally authorized to make decisions on behalf of the pregnant woman or the fetus, or if he is the legally recognized guardian of the pregnant woman.

In some cases, the father's involvement in the informed consent process may be required by law or by the policies of the institution conducting the research. For example, some institutions may require the father's consent if the research involves interventions that could affect the father's health or if the research involves genetic testing or screening that could have implications for the father or the baby.

However, in other cases, the father's involvement in the informed consent process may not be necessary or may not be possible. For example, if the father is not available or cannot be located, or if the pregnant woman is not legally married or does not have a legally recognized partner, then the informed consent process may proceed without the father's involvement. Ultimately, the decision about whether or not to involve the father in the informed consent process will depend on the specific circumstances of the research study and the applicable legal and ethical requirements.

In addition, the regulations state that if the research involves pregnant women who are minors, the consent of the pregnant woman and her legal representative must be obtained. If the pregnant woman is unable to provide consent, the regulations provide guidance for obtaining consent from a surrogate decision-maker.

Overall, the special requirements concerning the consent of pregnant women prioritize the protection of the developing fetus while also allowing for important research to be conducted in this population when the benefits outweigh the risks.

Children

When it comes to involving children in clinical research, special considerations and protections must be taken into account to ensure their welfare and rights are protected. In general, children under the age of 18 are considered minors and cannot legally give informed consent to participate in research. Therefore, obtaining consent from a parent or legal guardian is typically required. However, in some cases, children who are considered "mature minors" may be able to provide their own informed consent if they have the cognitive and emotional capacity to do so.

The specific requirements concerning the consent of children in clinical research depend on the regulations of the country or region in which the study is taking place. In the United States, the regulations governing the participation of children in research are outlined in the Department of Health and Human Services' Code of Federal Regulations, specifically 45 CFR part 46. Additional requirements may also be set forth by institutional policies, funding agencies, and professional organizations.

Some of the key special requirements concerning the consent of children in clinical research include:

1. Involvement of parent(s) or legal guardian(s): Consent from a parent or legal guardian is typically required before a child can participate in research. The consent process should be tailored to the child's age and developmental level, and efforts should be made to ensure that the parent(s) or legal guardian(s) understand the nature of the study and the potential risks and benefits.
2. Assent from the child: Even if the parent or legal guardian provides consent, the child should be given the opportunity to provide assent to participate in the study if they are capable of understanding the nature of the research and its implications. The level of assent required will depend on the child's age, maturity, and cognitive ability.
3. Ethical considerations: When designing studies involving children, ethical considerations should be carefully considered to ensure that the research is conducted in a way that is in the best interests of the child. Special attention should be paid to issues related to risk and benefit, confidentiality and privacy, and protection of vulnerable populations.
4. Regulatory requirements: Researchers should be aware of the regulatory requirements governing the participation of children in research, including any additional requirements that may be imposed by funding agencies, institutional policies, or professional organizations.

Prisoners

Special requirements and protections are in place for conducting research involving prisoners as participants. These requirements are designed to safeguard the rights and welfare of prisoners, who may be vulnerable to exploitation or coercion.

45 CFR 46.303 defines a prisoner as "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."

Under federal regulations, research involving prisoners is allowed only if the research meets specific conditions, including:

1. The research must be aimed at obtaining generalizable knowledge that cannot be obtained through other means.
2. The research must pose no more than minimal risk to the prisoners.

3. The research must not involve procedures that are medically risky or that would affect the length or conditions of the prisoners' confinement.
4. The research must not involve vulnerable subpopulations of prisoners, such as pregnant women or those with mental disabilities.
5. The prisoners must be selected equitably for participation in the research, and the selection process must not involve coercion or undue influence.
6. Informed consent must be obtained from the prisoners, and additional safeguards must be put in place to ensure that the prisoners are fully informed about the risks and benefits of participation and that they are not coerced or unduly influenced.
7. The researcher must obtain approval for the research from the Institutional Review Board (IRB) that is responsible for reviewing research involving prisoners.

Overall, the special requirements concerning the consent of prisoners require that researchers take additional precautions to ensure that prisoners are not exploited or coerced into participating in research, and that their rights and welfare are protected.

The Informed Consent Process

To be valid, informed consent must be based on the following:

Capacity to Give Informed Consent: One of the key requirements of the informed consent process is that the participant must have the capacity to give informed consent. This means that the participant must have the ability to understand the information provided to them about the study, and the implications of participating in the study. They must also be able to make a rational and informed decision about whether or not to participate. This capacity may be affected by a number of factors, including the participant's age, cognitive ability, and mental health status.

Disclosure of all Relevant Information: Another key requirement of the informed consent process is that all relevant information about the study must be disclosed to the participant. This includes information about the purpose of the study, the procedures involved, the risks and benefits of participating, and any alternatives to participation. This information must be provided in a clear and understandable way, and in a manner that is appropriate for the participant's level of comprehension.

Comprehension by the Participant: In addition to disclosing all relevant information, it is also important to ensure that the participant has a good understanding of the information provided. This means that the information must be presented in a way that is easily understood, and that the participant has had the opportunity to ask questions

and have them answered. If the participant does not fully understand the information provided, the informed consent process may not be valid.

Voluntary Agreement by the Participant: The informed consent process must also ensure that the participant has given their voluntary agreement to participate in the study. This means that the participant must not be coerced or unduly influenced to participate in the study, and must be given the opportunity to freely decide whether or not to participate. This requires that the participant be provided with enough time to consider their decision, and that they are given the opportunity to withdraw from the study at any time.

Right to Withdraw: Finally, the informed consent process must ensure that participants are informed of their right to withdraw from the study at any time, without any penalty or negative consequences. This means that participants should be made aware that they can withdraw from the study at any time, and that this decision will not affect their future medical care or treatment. Participants should also be informed of the process for withdrawing from the study, and who to contact if they decide to withdraw.

Inviting Potential Participants to Enroll in a Research Study

When inviting participants to participate in a research study, there are some questions that one should have in mind to ensure that the informed consent process is valid.

Is the participant capable of understanding information about the study and giving informed consent voluntarily?

An adult is considered capable of giving consent if they have the ability to understand the nature of the research study, appreciate the risks and benefits of participating, and make a voluntary decision to participate or not.

Several factors can affect an adult's capacity to give consent. For example, individuals with cognitive or developmental disabilities, mental health conditions, or substance use disorders may have difficulty understanding the information presented to them or making an informed decision about participation. Additionally, advanced age or medical conditions that affect cognitive function may also affect a person's ability to understand and make decisions about participating in research.

In some cases, temporary or situational factors, such as pain, anxiety, or stress, may also affect a person's ability to give informed consent. It is the responsibility of the researcher or healthcare provider to assess the potential participant's capacity to give

informed consent and take appropriate steps to ensure that they fully understand the study and are making a voluntary and informed decision to participate.

If an individual is unable to provide informed consent, a legal representative may give permission for them to participate in research in some circumstances. A legal representative may be:

1. A court-appointed guardian or conservator who has the legal authority to make decisions on behalf of the individual.
2. A person designated by a court to make decisions on behalf of the individual, such as a legal guardian or next of kin.
3. A person who has durable power of attorney for healthcare decisions for the individual.
4. A person authorized by statute to make decisions on behalf of the individual, such as a parent or legal custodian of a minor.

The specific requirements for who can act as a legal representative and the process for obtaining their consent may vary depending on the laws and regulations of the jurisdiction where the research is being conducted.

Has the participant been given sufficient, accurate information about the study?

To ensure that a participant has been given sufficient, accurate information about a study, a member of the research team should:

1. Provide a clear and understandable explanation of the study in a language and manner that the participant can comprehend.
2. Answer any questions the participant may have about the study, including risks and benefits.
3. Use visual aids or other educational materials, if needed, to help the participant understand the study.
4. Provide the participant with a copy of the informed consent document to review and keep for their records.
5. Encourage the participant to ask questions and take time to consider their decision before agreeing to participate in the study.
6. Ensure that the participant understands that their participation is entirely voluntary and that they have the right to withdraw from the study at any time without penalty.
7. Document the informed consent process, including any questions or concerns raised by the participant and how they were addressed, in the participant's medical record.

To ensure that potential participants fully understand information about a study, it is crucial to present the information in a language that they comprehend and at a pace that they can follow. Additionally, the information must be presented in a way that welcomes questions. When presenting information to a group of potential participants, it is important to meet with each person individually to provide them with the opportunity to ask questions privately.

Does the participant understand the information he or she has been given about the study?

To ensure that potential participants fully understand information about a study, it is crucial to present the information in a language that they comprehend and at a pace that they can follow. Additionally, the information must be presented in a way that welcomes questions. When presenting information to a group of potential participants, it is important to meet with each person individually to provide them with the opportunity to ask questions privately.

When a participant has limited speaking ability in English, it is important to ensure that the information about the study is presented to them in a language they can understand. This may involve providing written materials in the participant's preferred language or using an interpreter who is fluent in both English and the participant's preferred language. The interpreter should be independent, trained, and able to maintain confidentiality. It is also important to ensure that the participant has ample time to ask questions and clarify any misunderstandings.

When a participant has limited reading ability, the research team should make sure that the informed consent document is available in a format that is accessible and understandable to them. This could include using larger fonts, simple language, visual aids, and audio recordings. Additionally, the research team should ensure that the participant has enough time to review and understand the information, and should provide opportunities for the participant to ask questions and seek clarification. In some cases, it may be necessary to engage a translator or interpreter to assist with communication. It is important to ensure that the participant fully understands the information before obtaining their informed consent to participate in the study.

Is the participant’s decision to participate in the study entirely voluntary or has he or she been coerced or influenced in any way (e.g., by circumstances or by other people)?

In the informed consent process, it is important to ensure that the participant's decision to participate in the study is entirely voluntary and free from any coercion or undue influence. Coercion can occur if the individual feels compelled to participate due to the threat of harm or punishment or financial pressure. Vulnerable individuals in relationships of dependence or unequal power may be particularly susceptible to coercion. Blatant forms of coercion and coercive financial incentives are rare today due to the watchfulness of research teams and IRBs. However, subtle and unintentional coercion can still occur, which can be more difficult to detect. Therefore, it is crucial to be vigilant and ensure that participants are making informed decisions without any undue influence.

Does the participant understand that signing the informed consent document indicates agreement to participate in the study?

The act of signing the informed consent document serves as an indication that the participant has comprehended the information about the study and is willing to participate. It is the final step in the informed consent process. The research team member who conducts the informed consent discussion must sign the form, confirming that the participant has understood the study and is volunteering without any coercion. The process of obtaining informed consent should follow the procedures authorized by the local IRB. According to ICH GCP, the person conducting the informed consent discussion should also sign the form. The participant should receive a copy of the signed consent document, while the original must be kept on file in the research offices following the local IRB guidelines.

Quality Control in the Informed Consent Process

The main aim of the informed consent process and IRB is to safeguard human research participants. Failure to follow the guidelines for informed consent and proper documentation can lead to the suspension of the study. Any errors in the informed consent process are considered protocol violations and must be reported to the relevant IRBs, with actions taken to correct and prevent them from recurring. Severe or ongoing violations may result in penalties and reporting to regulatory authorities. To prevent errors, it's crucial to carry out the informed consent process with attention to detail. This section highlights common errors that can happen and how to prevent them. In case of any mistakes, it's essential to address them honestly and immediately report them to the study staff to prevent them from occurring again.

Common mistakes that happen during the informed consent process

The situation where **a participant signs the informed consent form after study procedures have begun** is an error that may occur during the informed consent process. For example, a staff member who is eager to assist may ask a client to fill out forms without checking if they have gone through the informed consent interview. Later, another staff member may assume the participant has completed the informed consent documentation and enroll them into the study without verifying.

To prevent this error, it is important to never assume and always check that a participant's informed consent documentation is complete before starting any study procedures. Study assessments should not be performed until informed consent has been obtained.

If such a mistake occurs, corrective action should be taken immediately. This includes reviewing the study and consent form with the participant as soon as possible, documenting all steps taken to correct the situation, attaching the documentation to the signed Informed Consent Form, and notifying a supervisor.

Another error that might occur is when **the consent form is missing the signature or initials of the investigator or witness, or if it is not dated**. This could happen when the investigator becomes distracted or forgetful, and neglects to sign or initial the form as required, or to check that the participant has written the date next to their signature. It is the responsibility of the principal investigator to oversee the informed consent process and ensure that the participant is comfortable with the discussion, even if they delegate the task to other research staff members.

To prevent this error, consent interviews should be conducted in a quiet, separate room without distractions. The person obtaining consent must be present when the participant signs the form, and the investigator should never sign the form later or backdate it. A checklist can be created and used to ensure that all details in the informed consent process are completed.

One possible mistake is when **whiteout is used to correct errors on the consent form**. This error occurs due to a failure to follow Good Clinical Practice or Good Medical Record correction techniques. The use of whiteout is not appropriate for any research or medical record document.

To avoid this error, one should follow good documentation practices. If an error is made on the consent form, use Good Clinical Practice or Good Medical Record correction techniques, which involve crossing out the mistake without hiding the original entry, initialing and dating the correction, and entering the correct information.

Sometimes, **an out-of-date version of the consent form is used**. It is important to ensure that the most recent version of the Informed Consent Form is being used during the study. This error can happen when staff members use an outdated form, which may have been created during the study's developmental stages or prepared after one year into the study. It is essential to identify the current version of the consent form with an identifiable mark or a date stamp and store it separately from older versions. Old and unused forms should be discarded, and the original copy of the old consent form must be marked as obsolete in the regulatory binder.

If an outdated form is mistakenly used, the corrective action is to reconsent the participant using the appropriate and current Informed Consent Form. Additionally, attach a memo describing the issue and corrective measures taken to the new consent form.

Another common mistake is when **participants missed signing a new consent form when it is required**. Whether it's because they were absent during the week when most participants signed the form or a staff member mistakenly assumed that another colleague had already taken care of it, this

To prevent this error, it is important to check with each participant during their next clinic visit to ensure that they have signed the new form. A system should be implemented to flag the files of participants who have not yet signed the new form, such as a tracking spreadsheet. Documentation of the consent form should be kept in the source notes.

When the issue is identified, the participant should be asked to review, sign, and date the new consent form. The reason for the delay should be documented and attached to the new consent form.

There may be a time when **the original consent form is missing**. The consent form may have been misplaced by staff or filed incorrectly. There is also the possibility that the participant was given the original form by mistake.

To prevent this error, establish and implement written procedures for handling informed consent documentation, and provide training to all staff involved in the process. If the original consent form is lost, promptly report the loss of the original consent form to the IRB and/or sponsor and obtain a new one as soon as possible. Ensure that the circumstances leading to the loss of the original form are thoroughly documented to prevent any suspicion of misconduct.

Requirements for the Documentation of Informed Consent

45 CFR 46.117 is a federal regulation that outlines the requirements for documenting informed consent in research studies involving human subjects. The regulation applies to studies that are supported by federal funding, conducted by federal agencies, or conducted by institutions that have agreed to follow the regulations.

The following are the requirements for the documentation of informed consent as set forth in 45 CFR 46.117:

1. Written Consent Document: A written consent document must be obtained from each participant, or their legally authorized representative, and must be signed and dated.

2. Essential Information: The consent document must include the essential information that a reasonable person would need to make an informed decision about whether to participate in the research. This includes the purpose of the research, the expected duration of the participant's participation, the procedures involved, and any risks or benefits associated with participation.

3. Voluntary Participation: The consent document must indicate that participation is voluntary and that the participant has the right to withdraw from the study at any time.

4. Alternative Procedures: The consent document must describe any alternative procedures or treatments that might be advantageous to the participant.

5. Confidentiality: The consent document must describe the extent to which confidentiality of records identifying the participant will be maintained.

6. Contact Information: The consent document must include contact information for the research team in case the participant has any questions or concerns.

7. Copies: The participant must be given a copy of the signed and dated consent document.

8. Language: The consent document must be in a language that is understandable to the participant or their legally authorized representative.

9. Updates: The participant must be notified of any significant changes in the research that may affect their willingness to participate.

10. Documentation: The researcher must maintain documentation of the informed consent process in the research records, including a copy of the consent document signed by the participant or their legally authorized representative.

In summary, the documentation of informed consent in research studies involving human subjects must follow the requirements set forth in 45 CFR 46.117 to ensure that participants are fully informed about the research and give their voluntary consent to participate.

21 CFR 50.27 outlines the requirements for the documentation of informed consent in FDA-regulated clinical trials. These requirements include:

1. Informed consent must be documented in writing: The informed consent process must be documented in a written consent form that is approved by the IRB and signed and dated by the participant or their legally authorized representative.

2. Consent form must contain certain elements: The consent form must contain all the elements required by 21 CFR 50.25, including a statement that the study involves research, the purpose of the research, the expected duration of the participant's involvement, the procedures to be followed, the risks and benefits of participating, alternatives to participation, and contact information for questions.

3. Consent form must be written in understandable language: The consent form must be written in language that is understandable to the participant or their legally authorized representative.

4. Participant or representative must receive a copy: The participant or their legally authorized representative must receive a signed and dated copy of the consent form.

5. Consent form must be updated: The participant or their legally authorized representative must be informed of any new information that may affect their willingness to continue to participate in the study, and the consent form must be updated to reflect any changes to the study.

6. Consent form must be retained: The consent form and any other documentation related to the informed consent process must be retained by the investigator for at least 2 years after the final marketing application is approved for the drug for the indication studied, or for 2 years after the last administration of the investigational drug to any participant, whichever is longer.

Overall, the requirements set forth in 21 CFR 50.27 aim to ensure that the informed consent process is well-documented, clearly communicated, and understandable to participants or their legally authorized representatives.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guideline 4.8 outlines the requirements for the documentation of informed consent in clinical trials. The key requirements are:

1. Informed consent must be documented in writing: The informed consent process must be documented in writing using a consent form that is approved by the Institutional Review Board (IRB) or Ethics Committee (EC). The consent form must be written in a language understandable to the participant and should include all the elements of informed consent.

2. Consent form should include key elements: The consent form must include the name and address of the investigator and the sponsor, a statement that the trial involves research, the purpose of the trial, the procedures involved, any risks and benefits, alternatives to participation, confidentiality of records, compensation for injury, and contact information for the investigator and the IRB/EC.

3. Consent form should be signed and dated: The participant or their legally authorized representative must sign and date the consent form. The date of consent should be clearly documented, and any changes made to the form must

be documented and initialed by the participant or their representative.

4. Copy of consent form should be given to participant: A copy of the signed consent form should be given to the participant or their legally authorized representative.

5. Consent form should be retained: The original signed consent form must be retained by the investigator and stored securely for the duration of the trial and a specified period of time after the trial ends, as required by applicable regulations.

6. Additional consent documentation: In some cases, additional documentation of the consent process may be required, such as audio or video recordings, or witness signatures.

7. Ongoing informed consent process: The informed consent process is an ongoing process, and the participant must be informed of any new information that may affect their willingness to continue participating in the trial. Any changes to the consent form must be approved by the IRB/EC and communicated to the participant.

Overall, ICH GCP 4.8 emphasizes the importance of thorough documentation of the informed consent process in clinical trials to ensure that participants are fully informed and protected throughout the study.

Chapter Three Resources

Summary of Key Points:

- Informed consent is the process of informing participants about a research study and obtaining their voluntary agreement to participate.
- The informed consent document should contain all the necessary information for participants to make an informed decision about participating in the study.
- The participant's signature on the informed consent document confirms their voluntary agreement to participate in the study.
- The general requirements for informed consent in federally funded research are outlined in 45 CFR 46.116 and 21 CFR 50.20, and some states have additional requirements.
- Researchers are responsible for ensuring that the informed consent process adheres to regulations and respects participants' right to make informed decisions voluntarily.

- The IRB must review and approve the consent document before the study can commence, and it should be written in a language that participants can understand.
- The information that must be provided in an informed consent document is specified in 45 CFR 46.116, 21 CFR 50.20, and ICH GCP 4.8.10.
- Additional protections for minors involved in research are set forth in 45 CFR 46 Subpart D.
- Participants must not be coerced or unduly influenced, and incentives for participation should not be so high that they are considered an undue influence.
- Complying with general requirements for informed consent and documentation is critical to avoid study suspension, fines, and penalties.

Confidentiality and Privacy in Clinical Research

Chapter Four

Confidentiality and Privacy

The confidentiality of research records containing participant identification is required to be maintained to the extent permitted by relevant laws and regulations. This includes the protection of participant identities in the publication of clinical study results, as mandated by federal regulations such as 45 CFR 46 and ICH GCP 4.8.10(o). Additionally, federal laws safeguard the confidentiality of individually identifiable health information for all research participants, as well as vulnerable populations and those undergoing alcohol and drug use treatment.

Apart from federal regulations, many states have their own laws and regulations to protect the confidentiality and privacy of individuals receiving healthcare. Researchers should be aware of these confidentiality and privacy provisions that apply in the state where their studies are conducted.

Confidentiality of Clinical Trial Participant Records

45 CFR 46 provides several protections for the confidentiality of research participants. These include:

1. Requirement for informed consent: Informed consent must be obtained from research participants before collecting any personally identifiable information.

2. Safeguarding records: Researchers must keep records confidential to the extent permitted by law, and must take measures to safeguard records against unauthorized access, use, or disclosure.

3. Limited access: Only authorized personnel should have access to research records, and records should be stored in a secure location.

4. Disclosure restrictions: Identifying information about research participants should not be disclosed without their explicit consent, except in certain circumstances such as when required by law or to prevent harm.

5. Data protection: When data is collected, it should be de-identified or coded so that it cannot be traced back to the individual participant.

6. Confidentiality agreement: Researchers must sign a confidentiality agreement, promising to protect the privacy and confidentiality of research participants.

7. Research participant rights: Research participants have the right to access their own records and to request that their records be corrected or amended if necessary.

Overall, 45 CFR 46 seeks to protect the privacy and confidentiality of research participants, while also allowing for the necessary collection and use of personally identifiable information in research studies. There are additional protections for research participants that are pregnant women, fetuses, or neonates, participants that are prisoners involved in biomedical and behavioral research, and participants that are children.

In addition to 45 CFR 46, the Health Insurance Portability and Accountability Act (HIPAA) mandates privacy protections for individually identifiable health information under 45 CFR 160 and 164. These regulations establish national standards for the privacy, security, and breach notification of protected health information (PHI) by covered entities, including health plans, health care clearinghouses, and health care providers that transmit PHI in electronic form.

HIPAA requires covered entities to obtain written authorization from individuals before using or disclosing their PHI for research purposes, with certain exceptions such as when the researcher signs a data use agreement with the covered entity or when a limited data set is used. The regulations also require covered entities to implement administrative, physical, and technical safeguards to protect the confidentiality, integrity, and availability of PHI, including policies and procedures for access controls, transmission security, and incident management.

HIPAA also provides individuals with certain rights related to their PHI, such as the right to access and receive a copy of their PHI, the right to request an amendment of their PHI, and the right to receive a notice of privacy practices. Covered entities are required to implement procedures to comply with these individual rights and to provide training to their workforce on the privacy and security of PHI.

In general, alcohol or drug use treatment programs cannot reveal that a specific person is a program participant, or disclose any information that identifies someone as a drug or alcohol user to people outside the program, unless the individual provides written consent, or a court order permits the disclosure, and the study or research location is not operating under a Certificate of Confidentiality.

A breach of confidentiality is usually defined as the unauthorized or unintentional disclosure of confidential or sensitive information. In the context of research, a breach of confidentiality occurs when the identity or personal information of a research participant is disclosed or released in a manner that is not consistent with the informed consent provided by the participant or with applicable laws and regulations governing the protection of participant privacy and confidentiality. A breach may include the accidental loss or theft of research data, the unauthorized access or disclosure of data by a researcher, or the failure to properly secure data storage and transfer.

Exceptions to Confidentiality Requirements

Certain exceptions to the confidentiality requirements for participant records in alcohol and drug use are recognized by federal regulations. Consider the following:

The "Need to Know" exception (42 CFR 2.12(c)(3)) allows for the disclosure of alcohol or drug use treatment records if it is determined that the recipient of the information has a legitimate need to know the information for purposes related to the provision of health care services to the patient. This exception applies to medical personnel who are treating the patient, but only to the extent necessary to provide treatment.

For example, a physician treating a patient for a medical condition that may be affected by the patient's substance use may need to know the patient's drug or alcohol treatment history in order to provide appropriate care. Similarly, a pharmacist may need to know about a patient's substance use to prevent drug interactions with prescribed medications.

However, this exception does not allow for the indiscriminate sharing of treatment records with all health care providers involved in a patient's care. The disclosure must be limited to those providers who need the information to provide appropriate care and

must be done in a way that protects the privacy and confidentiality of the patient's records.

Under **42 CFR 2.12(c)(5)**, a disclosure of information that identifies a patient as a drug or alcohol user may be made to appropriate law enforcement authorities if the program has reason to believe that the patient has committed a crime on the program's premises or against program personnel. The disclosure may only include the patient's name and address, and the nature of the alleged crime.

However, before making such a disclosure, the program must document the reasons for the belief that the patient has committed a crime and consult with its legal counsel to ensure that the disclosure is permitted under applicable laws and regulations. The program must also make a good faith effort to notify the patient that his or her information will be disclosed to law enforcement authorities, unless the program determines that such notification would be likely to result in substantial harm to the patient or others.

In addition, the program must limit the disclosure to the minimum amount of information necessary to achieve the purpose of the disclosure and ensure that the information is used only for the purpose for which it was disclosed. Finally, the program must record the disclosure in the patient's records, including the name of the law enforcement agency to which the disclosure was made, the date of the disclosure, and the nature of the information disclosed.

The regulation **42 CFR 2.12(c)(6)** allows for disclosure of alcohol or drug use participant records without the participant's written consent if there is suspected child abuse or neglect. This means that if a healthcare provider, counselor, or researcher suspects that a child is being abused or neglected and the abuse or neglect is related to the participant's alcohol or drug use, they can disclose relevant information from the participant's records to the appropriate state or local agency responsible for investigating such reports.

The disclosure can only include information that is necessary for the agency to conduct its investigation, and the person making the disclosure must document the reason for the disclosure and the information that was disclosed. The agency receiving the information must also be informed of the confidentiality requirements and must agree to protect the information and only use it for the purpose of investigating the suspected abuse or neglect.

It's important to note that the disclosure of information related to child abuse or neglect under this regulation is not mandatory but rather permissive, and it is up to the discretion of the healthcare provider, counselor, or researcher to determine whether the suspected abuse or neglect is serious enough to warrant a disclosure.

Under **42 CFR 2.2(e)**, a federally assisted alcohol or drug program may disclose confidential information to the Department of Veterans Affairs (VA) and the Department of Defense (DoD) for the purpose of providing medical benefits to veterans and members of the armed forces.

The disclosure must be limited to information necessary to carry out the VA or DoD programs, and the recipient must agree to abide by the confidentiality restrictions and limitations on redisclosure. The disclosure may only be made to VA or DoD personnel who have a need for the information in connection with their official duties.

The program must also notify the patient that their information will be disclosed to the VA or DoD and must include a statement about the restrictions on redisclosure. Additionally, the program must keep a record of the disclosure and the recipient’s agreement to abide by the confidentiality restrictions.

It is important to note that this exception only applies to federally assisted alcohol or drug programs and does not apply to private facilities or providers.

Under **42 CFR 2.51(a)**, a disclosure of alcohol or drug use participant records is permitted in the event of a medical emergency. This means that if the disclosure of participant records is necessary to provide medical care for the participant and the participant is unable to provide informed consent due to their condition, then the program may disclose the necessary information to the medical personnel involved in the emergency care.

The disclosure must be limited to the information necessary to provide the medical care and must be made only to medical personnel involved in the care. The program must document the disclosure in the participant's records, including the name of the medical personnel who received the information, the date of the disclosure, and the purpose of the disclosure.

It is important to note that this exception does not apply to disclosures for routine or ongoing medical care, only in the event of a medical emergency. Additionally, the

program must make a reasonable effort to obtain the participant's consent to the disclosure as soon as possible after the emergency situation has passed.

Under **42 CFR 2.52**, a substance use disorder treatment program may disclose confidential patient information for the purpose of conducting scientific research under certain conditions.

Firstly, the disclosure must be made to a researcher who is a part of a program of research that has been approved by either an Institutional Review Board (IRB) or an equivalent privacy board.

Secondly, the researcher must agree in writing to protect the confidentiality of the information and not to re-disclose it in any way that would identify the patient.

Thirdly, the disclosure must be limited to only the minimum necessary information required for the research purposes.

Finally, the program must document in writing the specific reasons why the disclosure is necessary, and the documentation must be kept in the patient's record.

It is important to note that under 42 CFR 2.52, disclosure for research purposes is only allowed if the patient's written informed consent has not been obtained. If the patient has given informed consent for the disclosure of their information for research purposes, then the requirements under 42 CFR 2.52 do not apply.

Under the **Confidentiality of Substance Use Disorder Patient Records regulations (42 CFR Part 2)**, certain exceptions allow disclosure of patient information without their written consent. One of these exceptions is for Audit and Evaluation Activities.

Audit and Evaluation Activities refer to activities conducted to monitor or evaluate the effectiveness or quality of substance abuse treatment programs, services or activities. These activities may be conducted by Federal, State, or local government agencies, or by third-party organizations or individuals under contract with these agencies.

To disclose patient information under this exception, the following requirements must be met:

- The disclosure must be made for the purpose of conducting an audit or evaluation of a substance abuse treatment program or service
- The entity conducting the audit or evaluation must have a written agreement with the program or service provider to protect the confidentiality of the patient information received
- The patient information disclosed must be limited to that which is necessary to conduct the audit or evaluation
- The patient information may not be used to initiate or substantiate any criminal charges against the patient, or to conduct any investigation of the patient
- The patient information may not be disclosed to any other person or entity without the patient's written consent, except as otherwise permitted by 42 CFR Part 2.

The purpose of this exception is to allow for quality improvement and evaluation of substance abuse treatment programs without compromising the confidentiality of patient information.

The circumstance of **"danger to self"** refers to situations where a patient's substance use disorder puts them at risk of harming themselves. In such cases, healthcare providers may disclose information related to the patient's substance use disorder without their consent in order to prevent harm to the patient.

Under **42 CFR 2.51 and 45 CFR 164.512(j)(4)**, healthcare providers are allowed to disclose information related to a patient's substance use disorder if they believe that the disclosure is necessary to prevent or lessen a serious and imminent threat to the patient's health or safety. This includes situations where a patient is at risk of self-harm or suicide as a result of their substance use disorder.

Healthcare providers are required to limit the disclosure to only the information that is necessary to prevent the harm, and the disclosure should be made only to individuals or entities that are able to take steps to prevent the harm. The patient's written consent is not required in these cases. However, the provider must document the reason for the disclosure, the information that was disclosed, and to whom it was disclosed.

It is important to note that healthcare providers should only use this exception when other alternatives are not available. Providers should also consider the potential consequences of disclosing the information, such as stigma or discrimination, and take steps to minimize these risks.

The circumstance for disclosure related to **"Danger to Others"** refers to situations where the patient poses a serious and imminent threat of harm to others. In such cases, the regulations under **42 CFR 2.51 and 45 CFR 164.512(j)(4)** allow for the disclosure of confidential information to third parties who can take steps to prevent or reduce the danger.

However, this type of disclosure is limited to only the information that is necessary for protecting the potential victims from harm. The disclosure should be made to those individuals or entities that are in a position to prevent or reduce the risk of harm, such as law enforcement agencies, family members, or healthcare providers.

Before making any disclosure, the program must carefully evaluate the seriousness of the threat and determine that it is necessary to disclose the confidential information to protect others from harm. The disclosure must also be limited to only the information that is essential for the intended purpose and must be made in compliance with all applicable laws and regulations. Additionally, the program should document the circumstances that led to the disclosure and the steps taken to minimize the risk of harm.

The **disclosure of a person's communicable disease status** is subject to certain circumstances that allow for disclosure to specific entities or individuals. In cases where a participant has a disease that presents a risk to public health, confidential information regarding the participant may be disclosed.

In general, the disclosure of a person's communicable disease status must be done in compliance with state and federal laws, regulations, and ethical guidelines. Laws may vary by jurisdiction, but they often require healthcare providers to report communicable diseases to public health authorities to protect public health.

Disclosure of communicable disease status may also be allowed in the context of medical emergencies or when there is a risk of harm to others. For example, healthcare providers may disclose a patient's communicable disease status to public health authorities, law enforcement, or other individuals if they believe there is a risk of harm to the public or specific individuals.

In research settings, the disclosure of communicable disease status may be necessary to protect research participants and staff. However, any disclosure must be done in compliance with applicable laws and regulations, and with appropriate protections for the privacy and confidentiality of the individual's health information.

A **court order** may authorize the release of confidential information about a participant in certain situations. These situations include when disclosure is necessary to protect against a threat to life or serious bodily injury, when it is necessary for the investigation or prosecution of a serious crime, or when it is relevant to a legal or administrative proceeding where the participant offers evidence related to the confidential information. It is important to note that a court order does not automatically require the disclosure of confidential information, and a subpoena or other legal mandate is required to compel the disclosure.

State laws can mandate certain disclosures of confidential information about a research participant. Researchers must be aware of state laws that apply to their studies and comply with them. In some cases, state laws may be more restrictive than federal laws, so researchers should be careful to follow the stricter requirements.

For example, some states may require disclosure of certain information related to communicable diseases or suspected child abuse or neglect. State laws may also require reporting of certain diseases to public health authorities. In these cases, researchers may be required to disclose confidential information about a participant to comply with state laws.

Researchers should also be aware that state laws regarding the confidentiality of medical and health information may apply to them. These laws may require additional protections for the privacy and confidentiality of research participants beyond what is required by federal law. It is important for researchers to familiarize themselves with state laws and regulations that apply to their studies and to ensure that they are in compliance with all applicable requirements.

Research participants should be informed about the limitations of a **Certificate of Confidentiality** (CoC) in protecting their privacy during a research study. Although the CoC provides protection against compelled disclosure in some situations, participants should be aware that it does not cover all circumstances mentioned above, and they should be informed of the specific conditions under which the certificate may not prevent disclosure of their information.

Maintaining Confidentiality of Research Participants

There are many ways to maintain the security of written records in a study trial:

1. Locking storage: Written records should be stored in locked cabinets or rooms with restricted access.

2. Limited access: Only authorized personnel should be given access to the written records. This can be achieved by providing keys or electronic access codes to those who are authorized to access the records.

3. Labeling and organizing: Written records should be clearly labeled and organized so that they can be easily retrieved when needed. This can help prevent loss or damage to the records.

4. Backups: Electronic copies of written records should be backed up regularly to prevent loss due to hardware failure, theft, or other unforeseen circumstances.

5. Disposal: Written records should be disposed of properly and securely when they are no longer needed. This can include shredding paper records or securely erasing electronic records.

6. Training: All personnel who handle written records should be trained on proper storage, handling, and disposal procedures to ensure the security and confidentiality of the records.

Written procedures should be adopted by each program to manage the access and usage of these records.

When a program is discontinued, participant records must be maintained and retained in accordance with federal and state regulations. The program must also ensure that appropriate safeguards are in place to protect the confidentiality of the records. If the program is transferring the records to another entity, they must obtain written consent from the participant before doing so. If the program is closing permanently, they must notify the participants and provide them with instructions on how to access their records. The program must also provide for the secure destruction of all records that are no longer required to be maintained.

Unless the subject of the records consents in writing to transfer the records to another designated program or unless the law requires the records to be retained for a specified period, the program must purge participant-identifying information from its records or destroy the records.

According to 42 CFR 2.19(b)(1), retained records must be securely stored in envelopes or other containers and held by a responsible person. This person is responsible for ensuring that the records are destroyed as soon as practicable at the end of the specified retention period. The records must be sealed to maintain their confidentiality and ensure that they are not accessed or used inappropriately. By following these procedures, the program can ensure that participant information is protected and that the records are disposed of in a secure and appropriate manner.

Maintaining the confidentiality of information disclosed by study participants is of utmost importance as researchers typically use information that has been voluntarily disclosed by participants with their informed consent for research purposes. The researcher-participant relationship is based on trust, thus ensuring confidentiality is crucial.

To maintain the confidentiality of research participants, the following routine practices are recommended:

1. Instead of using names and other identifying information, use substitute codes.
2. Remove face sheets that contain identifiers like names and addresses.
3. Dispose of paper documents that contain identifiers properly.
4. Restrict access to all participant-identifying data.
5. Provide education to research staff about the significance of maintaining confidentiality.
6. Keep paper records in locked cabinets.
7. Assign security codes to computerized records.

Certificates of Confidentiality

A **Certificate of Confidentiality (CoC)** is a legal document issued by the National Institutes of Health (NIH) that protects the privacy of research participants by prohibiting disclosure of identifiable, sensitive research information to anyone not connected with the research except when required by law. The CoC is intended to encourage participation in sensitive research by assuring participants that their privacy will be protected to the fullest extent possible. It applies to research that collects or uses information that, if disclosed, could have adverse consequences for the participants or damage their financial standing, employability, or reputation. The CoC is granted to researchers whose studies meet certain criteria, including those that collect information about drug or alcohol abuse, sexually transmitted infections, mental health, or illegal behavior.

- Transfer of a Certificate of Confidentiality from one researcher to another is not permitted.
- Each Certificate of Confidentiality has an expiration date, and if the research project cannot be completed by the expiration date, the researcher must request an extension in writing well before the expiration date.
- If significant changes occur in the research project, such as changes in personnel or the scope of the research, the Certificate of Confidentiality must be amended. This requires a written request detailing the changes before they are implemented.
- In a multi-site trial, one Certificate of Confidentiality may be applicable for all sites, but study investigators can contact the agency issuing the certificate through the CoC coordinator.

A Certificate of Confidentiality can be obtained from the National Institutes of Health (NIH) or other federal agencies that support research.

To apply for a Certificate of Confidentiality, researchers need to provide information about the research project and the participants, including the following:

1. A description of the research project and its objectives
2. The types of data that will be collected
3. The participants' characteristics, such as age and gender
4. The procedures for collecting, storing, and analyzing the data
5. The measures that will be taken to protect the confidentiality of the participants' information
6. A statement indicating whether informed consent will be obtained from the participants and the type of informed consent that will be used.

The application process may also require researchers to provide information about the funding sources for the research, as well as any potential conflicts of interest. Once the application is reviewed and approved, the researcher will receive a Certificate of Confidentiality, which can be used to protect the identifiable information of participants in the research project.

Participants must be informed about these aspects of the Certificate of Confidentiality:

- The Certificate of Confidentiality is a legal document that helps protect the privacy of research participants.
- The certificate prohibits researchers from disclosing any identifiable, sensitive information about participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level.
- The certificate covers all research activities, including data analysis, that involve the use of identifiable, sensitive information about participants.
- The certificate does not prevent participants from being required to disclose information about themselves in some situations, such as if they are asked to testify in a court proceeding or if there is a mandatory reporting requirement for certain types of abuse or neglect.
- The certificate does not provide absolute protection for participants, and there may be rare situations where a court could order disclosure of identifiable, sensitive information about them despite the certificate.
- Participants should be informed that the Certificate of Confidentiality is not a substitute for informed consent, and they should still be provided with information about the research study and asked to provide their informed consent before participating.
- Participants should also be informed that the Certificate of Confidentiality is not a guarantee of privacy, and they should be given information about the steps that will be taken to protect their privacy during the study.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule

What is the HIPAA Privacy Rule?

The HIPAA Privacy Rule is a federal regulation implemented in 2003 to protect the privacy and security of individuals' health information. HIPAA stands for the Health Insurance Portability and Accountability Act, which was passed by the US Congress in

1996 to improve the efficiency and effectiveness of the healthcare system and to protect the privacy and security of individuals' health information.

The Privacy Rule establishes national standards for the protection of certain health information, known as "protected health information" or PHI, that is held or transmitted in any form or medium. The rule applies to covered entities, which include health plans, healthcare clearinghouses, and healthcare providers that electronically transmit health information.

The Privacy Rule provides individuals with certain rights regarding their PHI, including the right to access and receive a copy of their PHI, the right to request corrections to their PHI, and the right to file a complaint if they believe their rights have been violated.

The Privacy Rule also requires covered entities to implement administrative, physical, and technical safeguards to protect the confidentiality, integrity, and availability of PHI, and to limit the use and disclosure of PHI to only the minimum necessary to accomplish the intended purpose of the use or disclosure.

In addition, the Privacy Rule requires covered entities to provide notice to individuals of their privacy rights and the covered entity's privacy practices, and to obtain written authorization from individuals before using or disclosing their PHI for certain purposes, such as marketing.

Violations of the Privacy Rule can result in significant penalties, including fines and criminal sanctions. The Department of Health and Human Services Office for Civil Rights is responsible for enforcing the Privacy Rule.

To whom does the HIPAA Privacy Rule apply?

The HIPAA Privacy Rule applies to "covered entities" and their "business associates." Covered entities are health plans, healthcare clearinghouses, and healthcare providers who transmit any health information in electronic form, while business associates are persons or organizations that perform functions or activities involving the use or disclosure of protected health information on behalf of a covered entity.

Health plans include individual and group plans that provide or pay the cost of medical care, including Medicare and Medicaid. Healthcare clearinghouses are entities that process health information received from another entity, such as a hospital or clinic. Healthcare providers include healthcare professionals such as doctors, nurses, and pharmacists, as well as facilities such as hospitals, clinics, and nursing homes.

Additionally, the HIPAA Privacy Rule also applies to any subcontractors of a covered entity or business associate that perform functions or activities involving the use or disclosure of protected health information, as well as to researchers who are conducting research involving protected health information.

What information is protected by the HIPAA Privacy Rule?

The HIPAA Privacy Rule protects all individually identifiable health information, known as protected health information (PHI), held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral. PHI includes information related to an individual's past, present, or future physical or mental health or condition, the provision of healthcare to an individual, and the payment for the provision of healthcare to an individual. Examples of PHI include a person's name, address, birth date, Social Security number, medical record number, or other identifier that can be used to identify a person, as well as information about the person's health condition, healthcare provided to the person, and payment for healthcare services. The Privacy Rule also applies to de-identified health information, which is health information that has been stripped of any information that could identify an individual.

Permitted Disclosures of Protected Health Information

The HIPAA Privacy Rule requires covered entities to limit their use or disclosure of protected health information (PHI) to the "minimum necessary" amount needed for treatment, payment, and health care operations, without obtaining the individual's authorization. There are a few exceptions to this rule, including:

- Use or disclosure of PHI by health care providers for treatment purposes.
- Disclosure of PHI to the individual who is the subject of the information.
- Disclosure of PHI to the Secretary of Health and Human Services, who has authority over the Privacy Rule.
- Use or disclosure of PHI that is required by law.

In some cases, covered entities may disclose PHI for certain "public policy" purposes without the individual's authorization, but they must keep a record of these disclosures for accounting purposes.

The HIPAA Privacy Rule permits covered entities to use or disclose protected health information (PHI) without the individual's authorization for the following public policy purposes:

1. Public health activities, such as reporting of disease, injury, or vital events, and public health surveillance, investigation, and intervention.
2. Victims of abuse, neglect, or domestic violence.
3. Health oversight activities, such as audits, inspections, and licensure.
4. Judicial and administrative proceedings, such as responding to a court order or subpoena.
5. Law enforcement purposes, such as identifying or locating a suspect, fugitive, material witness, or missing person.
6. Decedents, such as notifying family members, coroners, and medical examiners, and for research purposes.
7. Cadaveric organ, eye, or tissue donation.
8. Research in limited circumstances, such as preparing a research protocol, obtaining consent, or when required by law.
9. Serious threat to health or safety, such as preventing or reducing a serious and imminent threat to the health or safety of a person or the public.
10. Workers' compensation or similar programs, such as providing benefits for work-related injuries or illnesses.
11. When it is required by law.
12. For national security or intelligence activities.

Under the HIPAA Privacy Rule, covered entities are allowed to disclose protected health information (PHI) if they have obtained authorization from the individual. Authorization is a written agreement from the individual that allows a covered entity to use or disclose their PHI for a specific purpose that is not otherwise permitted under the Privacy Rule. The authorization must be written in plain language and clearly identify the individual and the information to be disclosed, as well as the purpose of the disclosure, the person(s) or entity(ies) to whom the information will be disclosed, and the expiration date. The individual has the right to revoke their authorization at any time, in writing, except to the extent that the covered entity has already taken action in reliance on the authorization. Covered entities must maintain the authorization in the individual's medical record and make it available to the individual upon request.

IRBs are required to guarantee the adequate protection of subjects' privacy and confidentiality of data in accordance with the Belmont Report.

The IRB is responsible for assessing if a research study could potentially invade the privacy of the subjects. The following factors should be taken into account during the assessment:

- The nature of the information that is being sought, and how private or sensitive it is.
- The likelihood that the study would be considered an invasion of privacy by the subjects.
- The significance of the research.
- The feasibility of alternative methods to carry out the study.

IRBs have the responsibility to assess if sufficient measures are in place to protect the confidentiality of collected information. Obtaining participant authorization for disclosures is a routine process during informed consent. This can be done by either combining it with the Informed Consent Form or through a separate authorization form. The following information must be included in the authorization:

- Description of information to be disclosed
- Identity of the person authorized to use or disclose information
- Identity of the person to whom information will be disclosed or used
- Purpose of disclosure or use
- Retention period for data with identifiers
- Expiration date of the authorization
- Participant's right to revoke authorization
- Statement that information disclosed may no longer be protected by the Privacy Rule
- Participant's signature and date of signature

Treatment programs are not required to track authorized disclosures, meaning that they don't need to document each occasion of disclosure once permission has been obtained from the participant. Good Clinical Practice guidelines mandate that obtaining informed consent adheres to federal, state, and local regulations and respects the voluntary, informed decision of the individual.

Sharing a Limited Data Set

Covered entities are permitted to use and disclose protected health information (PHI) included in a limited data set without requiring authorization or a waiver of authorization by entering into a data use agreement. However, limited data sets can only be used or disclosed for purposes related to research, public health, or health care operations.

The limited data set may contain specific identifiers such as admission, discharge, and service dates, birth date, date of death, age, and geographical subdivisions (such as state, county, city, precinct, or zip code).

- Clearly identify the person(s) or organization(s) authorized to receive or use the limited data set.
- Specify that the recipient must only use or disclose the data as permitted by the agreement or as required by law.
- Require the recipient to use appropriate measures to safeguard the data and to prevent unauthorized use or disclosure.
- State that the recipient must ensure that any agents or subcontractors also adhere to the same standards, restrictions, and conditions outlined in the data use agreement.
- Prohibit the identification of individuals whose information is included in the limited data set or any contact with them.

De-Identifying the Health Information

The process of removing individually identifiable health information from records or files is known as "de-identification," and covered entities are allowed to perform this to protected health information (PHI). De-identified health information is no longer subject to the HIPAA Privacy Rule as it does not contain individually identifiable health information.

Individually Identifiable Health Information

The HIPAA Privacy Rule defines individually identifiable health information as any information that pertains to an individual and could potentially be used to identify them. This includes the following:

1. Names.
2. Any geographic subdivisions that are smaller than a state, such as street address, city, county, precinct, or ZIP code. However, the initial three digits of a ZIP code may be used if the area contains more than 20,000 people. If an area contains 20,000 people or fewer, the initial three digits of the ZIP code must be changed to 000.
3. All elements of dates (except for the year) that relate to an individual, such as birth date, admission date, discharge date, date of death, and ages over 89. Elements of dates that indicate an age may be aggregated into a single category of age 90 or older.
4. Telephone numbers.
5. Fax numbers.

6. Email addresses.
7. Social security numbers.
8. Medical record numbers.
9. Health plan beneficiary numbers.
10. Account numbers.
11. Certificate or license numbers.
12. Vehicle identifiers and serial numbers, including license plate numbers.
13. Device identifiers and serial numbers.
14. Web URLs.
15. IP address numbers.
16. Biometric identifiers, such as fingerprints and voiceprints.
17. Full-face photographic images and comparable images.
18. Any other unique identifying number, characteristic, or code, unless it is allowed by the Privacy Rule for re-identification.

Obtaining a Waiver of Authorization for Certain Research Activities

If an Institutional Review Board or Privacy Board is satisfied that certain conditions are met, it may waive, either partially or completely, the requirement for an individual's authorization to disclose protected health information (PHI). These conditions include:

1. The use or disclosure of PHI poses minimal risk to individual privacy, and there is a plan in place to safeguard health information identifiers from inappropriate use or disclosure. Additionally, written assurances must be provided that the PHI will not be shared except as required by law, for authorized oversight of the research study, or for other research purposes.
2. The research could not be practically carried out without the waiver or alteration.
3. The research could not be practically carried out without access to and use of the PHI.

Privacy Board

A Privacy Board is a committee that can be established to consider requests to waive or alter the authorization requirement for the use and disclosure of protected health information (PHI) in a specific research study. It has the authority to waive or modify some or all of the authorization requirements for a particular research project or protocol. If a covered entity receives proper documentation of approval from a Privacy

Board regarding the waiver or alteration of the authorization requirements, it may use and disclose PHI without authorization or with an altered authorization.

Preparing a Research Protocol

If a researcher states in writing that the use or disclosure of protected health information (PHI) is solely for the purpose of preparing a research protocol, no PHI will be removed from the covered entity's location, and the PHI sought is necessary for the research, covered entities may use and disclose the PHI without authorization.

The Participant is Deceased

If a researcher submits a written statement declaring that the use or disclosure of protected health information (PHI) is solely for the purpose of research on deceased individuals, and the PHI is necessary for the research, covered entities may use and disclose the PHI without authorization. However, the covered entity must obtain documentation of the death of the individuals whose PHI is being sought.

HIPAA Rights, Privacy, and Enforcement

Two new rights for research participants are defined under the HIPAA Privacy Rule.

The Right to an Accounting

Under the HIPAA Privacy Rule, research participants have the right to request an accounting of their protected health information (PHI) that has been obtained under a waiver of or exception to the rule. This means that participants can ask researchers for a record of any disclosures of their PHI that have occurred over the past six years. However, there are certain circumstances in which a researcher is not required to provide an accounting.

Firstly, if a participant authorized the disclosure of their PHI, then the researcher is not required to account for it. Secondly, if the PHI was included in a limited data set, which

is a type of de-identified data that still contains some identifiable information, an accounting is not required. Thirdly, if the PHI was released as fully de-identified data, which means that all identifiers have been removed, then an accounting is not required either.

In addition, there are other situations in which an accounting is not required, such as for disclosures made for national security or intelligence purposes. Furthermore, disclosures made to correctional institutions or law enforcement officials do not require an accounting. However, it's important to note that in all cases where an accounting is not required, researchers must still comply with the other provisions of the HIPAA Privacy Rule to protect the confidentiality and security of participants' PHI.

The Right to Revoke Authorization

Under the HIPAA Privacy Rule, research participants have the right to revoke their authorization for the use and disclosure of their protected health information (PHI) at any time. The revocation must be in writing and submitted to the researcher or covered entity.

Once the authorization is revoked, the researcher or covered entity must stop using and disclosing the participant's PHI, except to the extent that they have already relied on the authorization to conduct research or take other actions. However, the revocation of authorization does not affect any disclosures that were made before the revocation.

It's important to note that the right to revoke authorization does not apply to uses and disclosures that are required by law, such as those for public health or law enforcement purposes.

Ensuring compliance with the HIPAA Privacy Rule and investigating complaints related to non-compliance is the responsibility of the DHHS Office of Civil Rights. Violations of the Privacy Rule may result in the imposition of civil or criminal penalties.

Chapter Four Resources

Summary of Key Points:

- Federal law and regulations mandate that participant records and identifiable health information in alcohol or drug use prevention, education, training, treatment, rehabilitation, or research must be kept confidential.
- Exceptions to the confidentiality requirement include diagnosis, treatment, and referral purposes, reporting suspected child abuse or neglect, medical emergencies, research purposes with certain conditions, and legal or state law requirements.
- When a program is discontinued or acquired, the site Principal Investigator must follow specific medical record retention period requirements.
- A Certificate of Confidentiality provides extra protection for research participants by preventing researchers from being compelled to identify them in any proceeding under certain conditions.
- The HIPAA Privacy Rule safeguards individually identifiable health information held or transmitted by covered entities and their business associates, referring to it as protected health information (PHI).
- Covered entities cannot use or disclose PHI except as allowed or required by the Privacy Rule, with certain exceptions for treatment, payment, and health care operations.
- PHI can be disclosed for research purposes with participant authorization obtained during the informed consent process.
- Health information that has been de-identified is not considered PHI and is not subject to the Privacy Rule.

Adverse Events and Keeping Participants Safe

Chapter Five

Safety and Reporting

The ICH Guideline for Industry: Clinical Safety Data Management discusses how participant safety is an essential aspect of Good Clinical Practice (GCP). It encompasses various issues, such as protocol design, quality-assurance monitoring, ethical considerations, and compliance with government regulations. Participant safety may require clinical judgment and decision-making that can vary among clinicians. Consequently, new researchers may feel overwhelmed by questions regarding participant safety.

Given the complexity of this topic, this chapter cannot address every possible participant safety concern that may arise during a clinical trial. Therefore, researchers should consult with the study investigator or other experienced team members for further guidance. This chapter also elaborates on the investigator's role in safeguarding research participants' well-being and safety.

Even after a clinical research study has obtained approval from an Institutional Review Board (IRB) or a Data and Safety Monitoring Board (DSMB) and after participants have given their informed consent, the responsibility to protect their well-being remains. Various entities are responsible for safeguarding the interests of study participants throughout the study duration.

In a clinical trial, it is not possible for a single person or organization to offer complete protection for the participants. Hence, there must be a well-organized and comprehensive plan for every trial to guarantee that all involved individuals comprehend and meet their respective duties.

Regular review of study data by research team members with sufficient knowledge of clinical trials, statistics, clinical disorders, and the Investigational Product under investigation is essential to ensure that adverse events are correctly reported and interpreted.

Continuous communication among all members of the research team is vital to maintain the safety of study participants.

Who bears the responsibility of ensuring the safety of participants in a study?

As per ICH GCP guidelines, the responsibility of making medical decisions related to the clinical trial rests with the investigator or a sub-investigator who is a qualified medical professional, such as a physician or a dentist, if required. It is the responsibility of the investigator to ensure that the subject receives appropriate medical care in the case of any adverse events and also to inform the subject when additional care is required for any intercurrent illnesses that come to their attention. (Ref: ICH GCP E6(R2), 4.3)

In studies of investigational new drugs, who bears the responsibility for ensuring the safety of participants?

The party accountable for adhering to the FDA regulations concerning participant safety in studies carried out under the Investigational New Drug (IND) regulations is the sponsor of the IND used in the study.

It is the responsibility of the investigator to safeguard the well-being, safety, and rights of participants who are under their care. The FDA mandates that investigators immediately report any unforeseen problems that pose a risk to participants or others to the Institutional Review Board (IRB). Additionally, investigators must notify both the sponsor and the IRB of any significant adverse events, regardless of whether they are related to the drug, and provide an evaluation of whether there is a reasonable chance that the drug caused the event.

Ongoing Informed Consent

As explained in the Informed Consent module, informed consent is not only a legal document, but also an ongoing process. Researchers are responsible for providing study participants with updated information regarding the safety of the product throughout the study, especially if any new developments or findings arise that may affect their willingness to continue participating. To achieve this, researchers must:

- Communicate any emerging developments in the study, relevant pre-clinical studies or related studies involving the same Investigational Product(s) to participants in a language they understand.
- Allow participants to ask questions about the information they receive.

- Ensure that participants are aware they can withdraw from the study at any time without facing any negative consequences.
- Confirm that participants fully comprehend the information they received and are making an informed decision to remain in the study voluntarily.

Participant Safety and Adverse Events

What is an adverse event?

According to The Good Clinical Practice (GCP) guidelines of the International Council for Harmonization (ICH), an **adverse event (AE)** is defined as any untoward medical occurrence in a patient or clinical study subject that does not necessarily have a causal relationship with the treatment being studied. This includes any symptom, sign, or laboratory abnormality that may be associated with the administration of the Investigational Product (IP), whether or not considered related to the IP. An AE can also refer to any event that occurs during the course of the study, regardless of whether it is related to the IP.

In the U.S. Code of Federal Regulations (CFR) Title 21 Section 312.32(a), an adverse event is defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

An adverse event (AE) can be any unfavorable or unintended sign, symptom, or disease that appears in an individual who has undergone medication, irrespective of the drug treatment's relationship with the occurrence. It can be a physical, psychological, or laboratory event such as a rash, depressed mood, or elevated blood sugar. Additionally, an AE can involve the aggravation of pre-existing symptoms or conditions, such as increased pain in a painful tooth. The term "adverse experience" may also be used interchangeably with "adverse event."

What is an adverse drug reaction?

The terms adverse event (AE) and adverse drug reaction (ADR) may be easily confused, but they have different meanings. While an AE refers to any unfavorable occurrence in a patient or clinical study participant, an ADR is an unfavorable occurrence resulting from treatment with a medicine or treatment.

According to FDA regulations, an ADR is an undesirable effect associated with the use of a drug that may be a predictable part of the drug's action or unpredictable. It is crucial to gather complete and clear information about every AE since while every ADR is an AE, not every AE is an ADR.

What is a serious adverse event?

An adverse event (AE) is deemed serious if it endangers the patient's life or functionality. The FDA describes a serious adverse event (SAE) as an unfavorable medical occurrence that results in death, is life-threatening, needs hospitalization or causes persistent disability, is a birth defect, or requires medical intervention to prevent any of the above outcomes. Only one of these criteria needs to be met for an AE to be categorized as serious. In some cases, changes in vital signs, laboratory or diagnostic test results may also be considered SAE if the alterations are significant enough to fulfill the above criteria.

It is essential to differentiate between severe and serious events. An incident may be severe, but it may not qualify as serious (e.g., Severe Migraine). Severity is discussed in this module. Additionally, elective surgery, such as planned hysterectomy, nose reconstruction, or removal of bunions on feet, does not qualify as a serious adverse event.

For instance, if a patient is diagnosed with pneumonia during a doctor's visit and given antibiotics to take at home, it is an AE but not an SAE. However, if the patient needs to be hospitalized for pneumonia, it is categorized as an SAE (i.e., pneumonia resulting in hospitalization).

What is an unexpected adverse event?

In clinical studies involving marketed drugs, the FDA considers an unexpected AE to be one that falls into one of two categories: either it is an AE that is not included in the drug's current labeling, or it is an AE that is more severe or specific than what is indicated in the labeling.

For clinical studies involving investigational new drugs, the FDA defines an unexpected AE as one of three things: either it is an AE that is not consistent with the information about the drug's risks in the relevant source documents (such as the protocol, Investigator's Brochure, and consent documents), or it is an AE that is not consistent

with the known risk information, or it is an AE that has occurred within the class of drugs, but not specifically with the Investigational Product.

What is an unanticipated problem?

According to the Office of Human Research Protections (OHRP), an unanticipated problem involving risks to study participants and others is an event that meets the following criteria:

1. It is unexpected in terms of nature, severity, or frequency, considering the research procedures outlined in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and the characteristics of the subject population under study.
2. It is related or possibly related to participation in the research. In this context, "possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the research procedures.

If an unanticipated problem is suspected, it must be promptly reported to the IRB, which will determine whether it should be reported to the appropriate regulatory authority. Although unanticipated problems are not defined in 45 CFR 46, all NIH-funded studies must comply with this regulation.

Assessing an Adverse Event

The protocol for a clinical study should outline a concise list of lab values, clinical signs, and symptoms that need to be addressed during each visit. Additionally, the protocol should define the timeline for collecting information on adverse events.

All AEs that occur in any clinical study participant should be assessed for severity and relatedness.

The severity and seriousness of an AE are not equivalent terms. Severity relates to the strength or magnitude of an event, such as mild, moderate, or severe pain, while the event may not have significant medical consequences, as with a severe toothache.

In contrast, the seriousness of an AE is measured by its impact on the patient's life or health status. Hence, an AE can be severe, like severe toothache, without being serious enough to threaten the patient's life or health.

Evaluating the severity of an AE is mainly dependent on the clinician's discretion. A universally recognized scale for assessing or quantifying the severity of AEs does not exist. It is crucial to involve a qualified physician or licensed medical personnel to determine the severity of an AE.

Whether an AE is associated with the study intervention is uncertain. A causal relationship between the AE and the intervention means that the intervention caused or is likely to have caused the AE. A time-related relationship between the intervention and the AE typically suggests such a relationship (e.g., the AE occurred shortly after the intervention was administered).

Evaluating the relatedness of the event to the study intervention is the responsibility of the clinician who examines and assesses the patient. Data managers who are not involved in patient clinical assessment should not undertake this crucial responsibility.

Acceptance that the AE is linked to the intervention generally necessitates a plausible mechanism of action, which involves a credible sequence of events that caused the AE. The Study Medical Monitor's opinion on this point may be useful to seek. Asking the participant if they think the intervention could have caused the AE may also be helpful.

If an AE is suspected to be caused by the intervention and raises concerns about the participant's safety, it is important to consider temporarily halting or permanently discontinuing the intervention. Rechallenging the participant by giving the intervention again to test the causal relationship is rarely done due to safety concerns, which makes it difficult to confirm whether the experimental intervention caused the AE.

To establish a causal relationship, the intervention may be discontinued and the participant rechallenged to see if the AE recurs. However, this is rarely done because of safety concerns, making it difficult to determine with certainty if an experimental intervention caused an AE.

When an AE is described as "associated with the use of the intervention," it means there is a reasonable possibility of a causal relationship based on the available evidence or arguments.

During the early stages of drug or intervention development when little is known about its safety profile, it is crucial to maintain a high level of suspicion for AEs and report any suspected AEs that may be related to the experimental intervention.

It is necessary to monitor and document any reported AE until it has resolved, and both the duration and severity of the event should be recorded. If an AE persists from one visit to the next, it should be documented as a single event, while for events that last beyond the study duration, follow-up should continue until resolution or for a reasonable time according to the protocol.

While participants usually report AEs initially, other sources such as family, friends, or caregivers may also report them. In any case, the event should be documented in the participant's source documents, including progress notes. When an AE is reported by a third party, the Research Assistant must confirm it with the participant directly to ensure accuracy. It is possible for some reports to be false, so as more information is gathered and assessed, source documents and reports should be updated with accurate information.

Adverse Event Reporting

Reporting adverse events (AEs) is a crucial aspect of ensuring participant safety during clinical studies. The determination of whether an incident qualifies as a reportable AE and what information should be reported, to whom, and when, depends on various factors such as prior experience and knowledge of the intervention or drug, the targeted disease, and regulatory obligations.

Besides these factors, investigators also need to consider the incident reporting standards set forth by NIH for its funded studies. This includes the obligation to report both reportable AEs and unanticipated problems (UPs) as per 45 CFR 46 guidelines for safety event reporting, which is applicable to all NIH-funded studies.

Reporting AEs is not always necessary, especially if they do not pose a direct risk to participants or provide significant new information. Reporting unanalyzed UPs individually to the study IRB can be uninformative, and non-risk-related UPs can be addressed during the IRB's continuing review. Each protocol outlines the requirements for AE reporting. When drafting the adverse event reporting sections of the protocol and operations manual, the investigator and research team must consider these factors. The extent and type of AE data collected for a specific trial is determined jointly by the investigators and the study sponsor. They may agree that minor daily complaints will not be categorized as AEs. The patient's progress notes or a case report form could capture an event such as a worsening of symptoms of a current illness.

ICH GCP (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice) guidelines provide internationally recognized standards for the design, conduct, monitoring, and reporting of clinical trials. ICH GCP guidelines define requirements for AE (adverse event) reporting in clinical trials. These requirements include:

1. AE Definition and Identification: Investigators must define and identify all AEs and serious adverse events (SAEs) that occur during a clinical trial. AEs and SAEs should be identified by an appropriate medical term, severity, and relationship to the study drug or intervention.

2. Reporting Procedures: Investigators must report all AEs and SAEs to the sponsor and the institutional review board (IRB) or independent ethics committee (IEC) in a timely and accurate manner, as defined in the protocol.

3. Expedited Reporting: Investigators must report all SAEs that occur during a clinical trial immediately to the sponsor and the IRB or IEC, as well as any regulatory authorities as required by local laws and regulations.

4. Causality Assessment: Investigators must conduct a causality assessment of all AEs and SAEs to determine if they are related to the study drug or intervention. This assessment should include consideration of the temporal relationship, alternative explanations, and the known safety profile of the drug or intervention.

5. Follow-Up and Documentation: Investigators must follow up on all AEs and SAEs until they are resolved and document the duration, severity, and outcome of each event. Documentation should be maintained in the study records.

6. Safety Reporting: Investigators must provide safety reports to the sponsor, IRB or IEC, and regulatory authorities on a regular basis, as defined in the protocol. These reports should include a summary of all AEs and SAEs that occurred during the reporting period, as well as any changes to the safety profile of the study drug or intervention.

The FDA guidelines (21 CFR 312.32) mandate that in IND studies, the sponsor must promptly report to the FDA all AEs that are related to the drug, unexpected, serious, and reasonably associated with the investigational product.

In the case of related and unexpected fatal or life-threatening AEs (severity grade 4 or 5), the sponsor must inform the FDA within 7 calendar days after the sponsor learns of the event. The initial report should be followed by a written safety report that is as comprehensive as possible within an additional 8 calendar days.

For serious, related and unexpected AEs that are not fatal or life-threatening, the sponsor must submit a written safety report to the FDA within 15 calendar days after the sponsor first learns of the event.

Additionally, the sponsor should report any relevant follow-up information for previously submitted reports to the FDA as soon as possible, including information about AEs that were not initially considered reportable if the follow-up information leads to a change in assessment.

If aggregate analyses of adverse events in clinical trials or studies outside the sponsor's scope reveal new information on the investigational product, such as new side effects or increased frequency, the FDA should be informed. Additionally, if significant non-clinical findings suggest an increased risk for human studies, they are also reportable. The FDA also accepts voluntary reporting for marketed drugs in studies that are exempt from their reporting requirements through the MedWatch system.

Expedited reporting to the FDA is generally not necessary for AEs that are serious but expected, serious but not related to the study drug (whether expected or not), or non-serious (whether expected or not). For example, if a patient dies of a pre-existing cancer during a study on an antidepressant, it would not be necessary to report it to the FDA as a serious AE.

In studies involving investigational new drugs, the FDA mandates that the sponsor informs all investigators in writing about any serious and unexpected AE associated with the drug's use. The sponsor may also impose additional requirements on this notification. If such an AE poses an escalated risk to study participants, investigators must notify them of the increased risk without delay.

Adverse Event Follow-up

Unless stated otherwise in the protocol, some networks have a standard practice of monitoring all adverse events (AEs) and serious adverse events (SAEs) that are not related to the study until they have resolved or stabilized. This monitoring period

typically lasts for 30 days after the participant's involvement in the study has ended, or until the condition has been resolved, whichever comes first.

It is crucial to closely monitor and follow up on all SAEs until the condition has resolved or stabilized with no further expected changes. As per the FDA's guidance, it is necessary to provide participants with appropriate medical evaluation and treatment until the emergent condition related to the study intervention has resolved, even if the follow-up period extends beyond the end of the study.

If a participant discontinues a study due to an SAE, investigators are advised to take the following steps:

1. The SAE should continue to be monitored until it resolves or stabilizes, as outlined in the study protocol.
2. The SAE and its follow-up should be documented in the participant's record.
3. Any final evaluations required by the study protocol should be attempted, if possible.
4. Medical evaluations should be performed to determine the cause of the SAE and its potential relationship to the study intervention. In cases of participant death, an autopsy report should be obtained if available.

In the case of a woman who discontinues a study due to pregnancy, the outcome of the pregnancy should be followed up until term. If the study involves an investigational drug known to carry the risk of birth defects, any information about birth or congenital abnormalities should be collected.

Losing participants who have ongoing SAEs can significantly impact the reliability of a study's results. Therefore, investigators should make every effort to contact participants who leave the study due to an SAE. The PI should maintain documentation of their attempts to do so.

The role of data and safety monitoring is crucial in safeguarding the safety of participants and upholding the validity of a research study. The goals of data and safety monitoring are as follows:

1. To minimize risks associated with clinical study participation to the extent possible.
2. To prevent exposing participants to undue risk.
3. To maintain the integrity of data collected in a clinical study.

4. To discontinue a study in the following circumstances: a. When safety concerns arise, or b. When the study objectives have been substantially achieved, according to predetermined criteria typically established prior to the commencement of the study.

It is important to bear in mind the following points regarding data and safety monitoring:

1. Regular data and safety monitoring should take place throughout all studies. The frequency of such monitoring depends on the risks associated with the study, as well as the size and complexity of the study. For instance, a small, single-site Phase I trial may require less frequent monitoring than a large, blinded, multi-site Phase III trial.
2. Periodic summaries of the data are created to evaluate if any changes or halting of the study are necessary. Any significant modifications to the study should be authorized by the local IRB and reported to appropriate institutional officials, the study sponsor, and the FDA (if the study involves an investigational new drug or device).
3. The risks and benefits of the study must be re-evaluated every time new study data is acquired.

Chapter Five Resources

Summary of Key Points:

- Clinical research studies must ensure the safety and well-being of participants at all times.
- An adverse event (AE) in a clinical study is any unintended medical occurrence that may or may not be related to the treatment being studied.
- For behavioral studies, an AE may be defined as any unfavorable, unintended symptom, diagnosis, or syndrome that occurs during the study and was not present at baseline, or that appears to worsen if present at baseline.
- Serious adverse events (SAEs) are AEs that pose a threat to the patient's life or functioning. The FDA defines SAEs based on specific criteria that include death, life-threatening situations, hospitalization, disability or incapacity, congenital anomalies or birth defects, and the need for medical intervention to prevent any of the above outcomes.
- Investigators in behavioral trials may modify or expand the FDA's SAE criteria to better reflect the intervention's risks and the study population's characteristics.
- The severity of an AE does not always correlate with its seriousness. A severe AE may not be serious and vice versa.

- SAEs should be reported immediately by phone or email and or into the EDC (Electronic Data Capture) system to all relevant parties as specified in the study protocol, including the FDA or other regulatory authorities if required.
- Reporting unanticipated problems that affect participant safety or others is required for NIH-funded studies, and OHRP provides guidance on determining, reporting, and reviewing such incidents.
- AEs and SAEs should be followed up until they have resolved or stabilized, and data and safety monitoring should occur periodically throughout the study to protect participants and ensure data integrity.

What is Quality Assurance in Clinical Research?

Chapter Six

What is Quality Assurance?

In clinical trials, Quality Assurance (QA) involves organized and methodical activities carried out to confirm that the trial is executed properly and that the trial data are created, recorded, and reported according to the protocol, Good Clinical Practice (GCP) guidelines, and any other relevant regulatory requirements.

Conducting research without adherence to high-quality standards can result in invalid data and put research participants at risk, making it unethical. The modules on Introduction, Institutional Review Boards, Informed Consent, and Participant Safety and Adverse Events discuss the protection of participants' safety, rights, and well-being. The U.S. Food and Drug Administration (FDA) conducts audits and identifies several common problems in research studies.

Quality data is crucial for the accurate interpretation of study results. Sloppy or incorrect data can lead to misleading conclusions, making it essential to pay careful attention to quality standards to ensure timely completion of studies. Completing high-quality studies in a timely manner helps bridge the gap between research and practice by bringing effective new treatments to clients more quickly.

The QA responsibility in a clinical trial is shared among all members of the protocol team. While it is common for CROs to handle QA and monitoring-related duties, the ultimate responsibility for implementing and maintaining QA systems lies with the sponsor. The sponsor is also responsible for overseeing any trial-related functions performed by other parties, such as a CRO or a subcontractor. All members of the protocol team, including investigators, are expected to carry out their duties diligently and thoroughly to ensure that the trial is conducted in compliance with the highest possible standards of quality.

The Monitoring Plan

The monitoring plan outlines the monitoring strategies, responsibilities of involved parties, monitoring methods, and the reasoning behind their selection. It also details the monitoring procedures, types of visits, their conduct, and the percentage of each document to be monitored. These procedures may be defined on a protocol basis depending on the study's design, purpose, size, complexity, and primary outcome measures (ICH GCP E6(R2) 5.18.3).

According to GCP guidelines, sponsors can choose between on-site monitoring, a combination of on-site and centralized monitoring, or centralized monitoring alone. Centralized monitoring processes can supplement or decrease the extent and/or frequency of on-site monitoring and differentiate between dependable and possibly unreliable data without complete source data verification (ICH GCP 5.18.3). The monitoring plan documents the rationale for the selected monitoring strategy.

Typically, on-site monitoring is necessary, and remote monitoring may occur at any research site before, during, and after the trial. Study monitors usually visit each site after enrolling one to two participants and schedule future visits based on various criteria, such as enrollment rate, data volume, site performance, and other factors.

Study monitors follow the monitoring plan's procedures and comply with Good Clinical Practice (GCP) guidelines when conducting site visits.

Quality Assurance and Monitoring Role

Monitoring Role for Sponsors

According to the Good Clinical Practice guidelines (ICH GCP 5.18.2), the sponsor is responsible for ensuring that monitors meet certain criteria, which include the following:

1. Monitors should be qualified and adequately trained with the necessary scientific or clinical knowledge to carry out the trial monitoring. The qualifications of the monitors should be documented.
2. Monitors should have a thorough understanding of the investigational product(s), the protocol, the informed consent form, and any other written information that will be provided to study participants, as well as the sponsor's Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

Quality Assurance (QA)/Study Monitor Role

The study monitors or QA personnel carry out the following study functions:

1. Initiation, interim, and closeout visits.
2. Centralized monitoring, if required.
3. Provide training on protocol-specific topics and Good Clinical Practice as needed or suitable.
4. Follow up on any problems discovered during prior monitoring visits.
5. Submit reports to the sponsor and other relevant parties as required.

ICH GCP 5.18.4 provides an in-depth explanation of the monitoring obligations:

1. Verifying that the investigator and study staff are performing the study as described in the protocol, the Investigator's Brochure (IB), and any other applicable regulatory requirements, and that any deviations from these documents are identified and documented and that appropriate corrective actions have been taken.
2. Ensuring that the investigator and study staff are adequately protecting the rights, safety, and welfare of study participants.
3. Verifying that the data generated and reported in case report forms (CRFs) and any other trial-related documents are accurate, complete, and verifiable from source documents.
4. Ensuring that CRFs and any other trial-related documents are kept up-to-date, and that any changes are made in accordance with the protocol and applicable regulatory requirements.
5. Reporting any suspected or confirmed breaches of the protocol, GCP, or applicable regulatory requirements to the sponsor, institutional review board (IRB), and/or regulatory authority(ies), as required.
6. Ensuring that the investigational product(s) are being appropriately handled, stored, dispensed, and accounted for at the site.
7. Verifying that the investigator and study staff are complying with the protocol, GCP, and applicable regulatory requirements with respect to any ancillary care and/or treatment provided to study participants.
8. Ensuring that study participants are enrolled and treated in accordance with the protocol and any applicable regulatory requirements, and that the study is conducted in compliance with GCP.
9. Ensuring that the investigator and study staff are adequately trained and that training is documented.

10. Ensuring that any problems or issues identified during monitoring visits are addressed in a timely and appropriate manner and that corrective actions are implemented.
11. Ensuring that the study is being conducted in accordance with the protocol, GCP, and applicable regulatory requirements.
12. Ensuring that the sponsor and other applicable parties receive timely and accurate reports regarding the conduct of the study.

Trial Monitoring Activities

Before the Trial

Site initiation:

Before a research site begins recruiting participants for a protocol, initiation visits take place after obtaining the necessary IRB approvals. During an initiation visit, study monitors ensure that trial documents are complete and in order, as well as inspect the facilities to ensure that the necessary work and storage space, equipment, medication, and supplies are available. They also ensure that adequate staff is available and trained properly. A list of documents to be retained by sites can be found in ICH GCP Section 8.

In addition, study monitors document any action items that the site needs to perform prior to site activation, and research sites are not allowed to start recruiting participants until the Investigator(s) and sponsor have provided approval.

During the trial

Routine monitoring visits:

The Monitoring Plan outlines the requirements for ongoing trial monitoring. Typically, monitors carry out the following tasks during the trial:

- Evaluate the trial's progression.
- Ensure that the trial is being conducted in accordance with the approved protocol/amendment(s), Good Clinical Practice (GCP) guidelines, and relevant regulatory requirements.
- Verify that participant welfare and rights are being safeguarded.

- Confirm the accuracy, legibility, contemporaneity, originality, completeness, and attribution of reported trial data, including source documents. All data should be traceable to source documents.
- Confirm that the site has the necessary resources to continue the trial.

During an interim site visit, specific monitoring functions include:

- Verifying the procedures for enrolling, assessing, treating, and following up with trial participants, which includes reviewing to ensure that:
    - Informed Consent forms are completed properly and are up to date.
    - Participants are screened and enrolled appropriately.
    - Inclusion and exclusion criteria are applied correctly.
    - Randomization procedures are followed, and the blind is maintained.
    - Trial assessments and treatment are conducted in compliance with the protocol.
    - CRFs are accurately, completely, legibly, and verifiably filled out based on the participant's source documentation.
    - All source documents are attributable, legible, contemporaneous, original, accurate, and complete.
    - Medication dosing and documentation are compliant with the protocol.
    - All adverse events and serious adverse events are documented and reported appropriately to the Sponsor, Lead Investigator(s), and IRB.
- Reviewing drug accountability records to ensure completeness and accuracy.
- Checking for any changes in procedures or staffing that have occurred at the site since the previous visit. For example, if a new Research Assistant or Site Coordinator has joined the research team, the monitor must verify that they have received all the required training.
- Checking for any protocol deviations/violations that may have occurred.
- Following up on any unresolved issues from previous visits.
- Providing, or arranging for, additional staff training in problem areas.

During an interim site visit, monitors may choose to review any or all of the following documents and research activities:

- Contents of the Regulatory or Essential Documents binder, with particular attention given to documents with expiration dates.
- Site logs.
- Informed consent forms and participant enrollment records.

- Records of drug accountability, including procedures for storing and dispensing the trial drugs.
- Compliance with the study protocol.
- Reports of adverse events and serious adverse events.
- Case report forms and source documents for individual participants.
- Protocol violations, deviations, and waivers.
- Staff adherence to rules and guidelines for data submission and correction.
- Laboratory procedures.
- Site facilities and recruitment procedures.
- The ability of the site and its staff to continue conducting the trial safely and in accordance with the protocol.

After the trial

Closeout

After completion of a trial, study monitors are required to conduct a closeout site visit to ensure the following:

- Finalization of drug accountability records.
- Disposal of unused medication as per the study sponsor and regulatory requirements (see 21 CFR 312.59) or its return.
- Return of all sponsor-provided trial equipment and supplies to the sponsor and/or supplier.
- Resolution of all data queries.
- Completeness of all trial documentation for storage, and the sponsor has been notified of their final storage location.
- Filing of notice of trial closure and all necessary reports with the appropriate entities (e.g., the sponsor and Institutional Review Boards).

Chapter Six Resources

Summary of Key Points:

- Quality Assurance (QA) involves planned and systematic activities aimed at ensuring that a clinical trial is conducted in compliance with the protocol and Good Clinical Practice (GCP), as well as all other applicable regulatory

requirements. This includes generating, documenting, and reporting trial data accurately.

- Every member of the research team is responsible for QA. QA staff supports and assists the team members in adhering to high-quality standards.
- Monitoring serves to verify the protection of human participants' rights and well-being, as well as the accuracy and completeness of trial data. Monitoring also ensures that the trial is conducted in compliance with the currently approved protocol, GCP, and all other applicable regulatory requirements.
- Monitoring can be performed on-site or remotely (via centralized monitoring) and is necessary before, during, and after the completion of a trial.

The Research Protocol and Standardization

Chapter Seven

What is the Research Protocol?

Ensuring Standardization

In a clinical research study, standardization is of utmost importance, especially for multisite trials. Conducting research in a non-standardized manner is unethical as it can jeopardize the safety of participants and produce invalid data.

To ensure that a research study is conducted in a standardized manner, several documents are essential. All research staff involved in a clinical study must be aware of these documents and strictly follow the procedures outlined in them.

The **Investigator's Brochure** is a document that includes clinical and nonclinical information about the experimental intervention, which is usually a medication, that describes the prior experience with it.

The **operations manual** provides additional details on the procedures required to conduct the research and serves to "operationalize" the protocol.

An operations manual provides more specific information on how to carry out the procedures outlined in the research protocol. For instance, while the protocol may specify the need for urine samples at each study visit, the operations manual would provide details on how to collect, label, store, and ship the samples. Similarly, the manual might require each study site to maintain a site contact log with names, addresses, and phone numbers of all individuals involved, and provide more detailed information, such as a list of staff responsible for maintaining the log and the procedures involved. The protocol itself would not include such specific details.

The **Standard Operating Procedures (SOPs)** provide detailed instructions on how to perform specific procedures, such as taking vital signs, conducting urine tests, and assessing adverse events in the research study. While most SOPs will be the same for

all study sites, site-specific variations may be necessary in certain situations. For instance, if procedures for handling a medical emergency differ slightly from one research site to another, the SOP for that particular site will reflect those variations. In addition, staff at each site will need to be trained accordingly for the site-specific procedures.

The current module's main focus is the **research protocol**. Other accompanying documents, such as the Investigator's Brochure, may contain additional information. Site-specific information that may vary during the trial, such as research site names and addresses and sponsor medical expert information, may be provided in a separate document known as the operations manual. As long as the protocol includes language referencing the operations manual for this information, such separation is acceptable.

Approval by the Institutional Review Board (IRB) is required before the research can commence, as the research protocol outlines the key elements of the proposed research. The IRB must also approve any modifications made to the protocol.

What makes the research protocol critical?

The Institutional Review Board must approve the research protocol before commencing any research study. It is also mandated by the Good Clinical Practice (GCP) guidelines of the International Council for Harmonization, as well as by Title 21 Part 312 of the Code of Federal Regulations (21 CFR 312) for studies conducted under an Investigational New Drug application. The research protocol outlines the essential aspects of the proposed research, and any amendments made to the protocol must also receive approval from the IRB.

Contents of the Research Protocol (ICH E3 GCP 6)

The **research protocol** is responsible for clearly and concisely defining the following elements of a research study:

1. The purpose of the study
2. The procedures that will be carried out during the study
3. The location of the study (for multi-site trials, site-specific information may be included in local protocol versions)

4. The individuals or groups involved in the study
5. The timing of the study interventions.

The protocol should provide sufficient information to convey a comprehensive and understandable overview of the study, without going into unnecessary specifics. As previously mentioned, additional details can be included in supplementary documents like the operations manual, standard operating procedures, quality assurance plan, training plan, and data management plan.

A sponsor may create a standardized template for investigators to utilize for each type of research study to guarantee that the research protocols contain the correct sections and content.

The protocol generally covers these topics:

Under the section of General Information, the protocol includes the following details:

- Title of the protocol, along with its identifying and version number, as well as the date of the current version.
- Contact information of the sponsor and monitor, if different from the sponsor, including their names and addresses.
- Name and designation of the person authorized by the sponsor to sign the protocol and its amendments.
- Names and designations of the investigators who will conduct the study, along with the address and phone number of the trial sites.
- Contact information of the sponsor's medical expert, including their name, title, address, and phone number.
- Details of the qualified physician who will be responsible for making all medical decisions related to the study, including their name, title, address, and phone number.
- Names and addresses of all institutions involved in the study, including clinical laboratories and other medical or technical departments.
- Addresses and phone numbers of all clinical laboratories and/or institutions participating in the trial.

The section on Background Information in the protocol includes the following details:

- A description of the issue that the study aims to address and its significance in terms of public health.
- Any findings from clinical or nonclinical studies that may be relevant to the proposed study.
- A summary of the potential risks and benefits of the study for human participants.
- A statement that the trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements.
- A description of the study population.
- References to relevant literature and data (which may be compiled in a separate section of the protocol).
- If the study involves the use of an investigational product or therapy, the protocol should include the name and description of the product or therapy, as well as the route of administration, dosage, dosage regimen, and treatment period(s), along with a justification for each.

The study objectives and purposes should be described in detail, including both the major (primary) and minor (secondary and exploratory) objectives, as well as the purpose of the trial.

The study design section of the protocol is crucial as the study design determines the scientific validity and reliability of the data obtained from the study. The following aspects should be described:

- The primary and secondary endpoints and how they will be measured.
- A schematic diagram of the study design, including procedures and stages, and whether the study is double-blind.
- Measures to reduce bias, such as randomization and blinding.
- The dosage, dosage form, packaging, and labeling of the investigational product.
- The expected duration of participant participation, including follow-up, and any stopping rules or discontinuation criteria.
- Accountability procedures for the investigational product, including placebos and comparators.
- Procedures for maintaining study treatment randomization codes and breaking codes if necessary.
- Identification of any data recorded directly on case report forms (CRFs) and considered source data.

A section on "Selection and Withdrawal of Participants" should include the following information:

- Inclusion and exclusion criteria for participants.
- Procedures for withdrawing participants, including:
    - Circumstances under which participants may be withdrawn from the study or investigational product treatment, and the process for doing so.
    - Details about the type and timing of data to be collected for participants who are withdrawn from the study.
    - Whether and how participants will be replaced.
    - Follow-up procedures for participants who are withdrawn from trial treatment.

The Treatment of Participants section outlines the treatment plan for participants in the study, including pharmacological and non-pharmacological interventions.

- Pharmacological treatment:
    - Details of all products to be administered.
    - Dose and dosing schedules.
    - Method of administration (e.g., oral, intramuscular).
    - Medications or treatments that are permitted or not permitted before and/or during the study, including rescue medication.
- Non-pharmacological interventions (e.g., chiropractic, physical therapy, social therapy, behavioral therapy, counseling):
    - Name of intervention (e.g., Motivational Interviewing, Cognitive Behavioral Therapy).
    - Frequency and duration of each session.
    - Method of each intervention (e.g., individual, group).
    - Treatment adherence.
- All interventions:
    - Duration of intervention and follow-up periods for participants in each group.
    - Procedures for monitoring participant compliance.
    - Identification of the individuals responsible for administering the intervention.

An Assessment of Efficacy section outlines the approaches to measure the efficacy of the treatment, which includes:

- Standards used to establish the treatment's effectiveness.
- Techniques and intervals for evaluating, documenting, and evaluating the effectiveness criteria.

The Assessment of Safety section outlines the procedures for monitoring the study and handling adverse events. It includes:

- Description of safety criteria.
- Methods and schedule for assessing, documenting, and analyzing safety criteria.
- Protocols for obtaining reports of adverse events and illnesses experienced by participants during the study period, as well as procedures for recording and reporting these events, including expedited reporting methods.
- Follow-up plan for participants who experience adverse events, specifying the type and duration of follow-up required.

The statistics section outlines the approach for analyzing the study data, which includes the following:

- Statistical techniques to be utilized, including the timing of any planned interim analyses.
- Total number of participants to be enrolled. (In multi-center studies, the minimum and maximum number of participants to be enrolled at each study site should be specified.)
- Rationale for the selection of sample size, including an assessment of the study's power and clinical justification.
- Significance level to be employed.
- Guidelines for halting the study.
- Protocols for accounting for absent, unused, and false data.
- Procedures for documenting discrepancies from the statistical plan (any discrepancies from the statistical plan should be explained and rationalized in the protocol and/or in the final report, as appropriate).
- Selection of participants for inclusion in analyses (e.g., all randomized participants, all dosed or treated participants, all eligible participants, all evaluable participants, per a stated definition of “evaluable”).

The protocol or any written agreement should specify that the sponsor ensures direct access to source data or documents for study investigators or institutions to permit monitoring, audits, IRB review, and regulatory inspections related to the study.

A comprehensive plan for quality assurance that outlines the established standards and measures in place to ensure adherence to the agreed-upon plan is typically presented as a distinct document. However, the protocol should provide an overview of the quality control procedures.

A comprehensive plan for quality assurance that outlines the established standards and measures in place to ensure adherence to the agreed-upon plan is typically presented as a distinct document. However, the protocol should provide an overview of the quality control procedures.

A comprehensive data management plan outlining the steps for collecting, documenting, verifying, submitting, and archiving study data is typically submitted as a separate document. However, the protocol should contain a general overview of the data management procedures related to the study. The data management plan should outline the measures in place to maintain data integrity across all study sites throughout the study, including:

- A description of the design and development of the data system.
- Data collection methods and activities.
- Methods for data entry and editing.
- Procedures for data monitoring (including resolving queries), reporting, and transfer.
- Data recipients and procedures for disseminating data.

The financing and insurance section of the protocol outlines how the study will be funded and insured. In certain research networks, these concerns may be covered in a separate agreement and therefore may not need to be included in the protocol.

The Publication Policy outlines the guidelines and procedures regarding the dissemination of the study results through publication. Some research networks may have established policies and procedures for researchers on the publication planning process. It is typically required that the primary outcome data be published before other study findings. Researchers should adhere to institutional and sponsor policies and requirements for publications.

Furthermore, in accordance with the Food and Drug Administration Amendments Act (42 CFR Part 11), trial results will be published on a public website, ClinicalTrials.gov. The website will not disclose the identity of the participants, but will serve as a resource for individuals seeking information about clinical trials.

The Supplements section provides any extra information that may be necessary based on the specific research being conducted. This may include attachments such as the informed consent template, therapy manual, patient information handbook, and other relevant materials.

What is a Protocol Amendment?

A protocol amendment refers to a written description of changes made to some aspect(s) of a study, as outlined in the research protocol.

To implement these changes, the designated Institutional Review Board (IRB) must receive a written submission of the protocol amendment and approve it before it is implemented. However, if the change(s) involve only administrative or logistical aspects of the trial (e.g., changing monitors, telephone numbers), or if there is an immediate hazard to the participants, the amendment may be implemented without IRB approval. In studies involving products regulated by the U.S. Food and Drug Administration (FDA), the amendment must also be submitted to the FDA before enacting it (21 CFR 312.30).

To ensure that study participants are kept informed, any changes made to the protocol must be communicated to them. In some cases, a revised Informed Consent Form may

need to be completed and signed by the participants, depending on the nature and extent of the amendment.

It is important to note that a protocol clarification is not the same as a protocol amendment. The former is intended to provide internal guidance and aid in the implementation or conduct of the study, without altering the risk-benefit ratio of the study. A clarification generally does not require submission to the IRB but should be provided in writing to all investigators.

What is a Protocol Violation?

Whenever a member of the study staff takes an action that does not align with the research protocol, it is considered a protocol violation. These violations are also commonly known as "protocol deviations." While the term "deviations" may suggest a lesser severity than "violations," the two terms have the same meaning.

A deviation from the research protocol, also known as a protocol violation, can occur due to various reasons such as inadequate study oversight, insufficient training of study personnel, or faulty site procedures. The violation can take various forms, such as omitting a required step, adding an unnecessary action, or changing a procedure outlined in the protocol. Although human error is a common cause, measures should be taken to minimize the occurrences of protocol violations. Any instance of protocol violation should be documented along with the remedial measures taken to correct the situation, and the report should be submitted to the IRB.

If there are repeated instances of protocol violation, it may indicate the need for additional training of research staff or require an amendment to the protocol to introduce more flexibility in the follow-up plan if participants are having difficulty adhering to it.

In case of a protocol violation, the following actions must be taken:

- Any safety issues related to the participants should be handled without delay by the study staff at the site.
- The violation should be recorded along with a plan of action to rectify it.
- The incident must be reported to the principal investigator at the site, the study investigator, project management (if applicable), and the sponsor. If the study is

under an IND, the FDA should also be informed, following the established procedures.
- The local IRB should be notified in a way that conforms to the IRB's documented procedures.

To avoid protocol violations, it is important to write a protocol that allows for flexibility without compromising the study's integrity or participant safety. Additionally, every member of the research team should be familiar with the protocol and the importance of adhering to it. To minimize protocol violations, the following steps should be taken:

- Thorough protocol training and periodic refresher training should be provided to all members of the study team.
- All members of the study team should be notified of any protocol amendments.
- Research materials such as the Informed Consent Form or Operations Manual should be updated to reflect changes in the protocol or procedures.
- Protocol requirements should be emphasized during regular study team meetings.

However, despite best efforts, protocol violations may still occur. In such cases, they must be documented and corrective actions should be taken to prevent them from happening again.

Chapter Seven Resources

Summary of Key Points:

- Standardization of procedures is necessary for ethical treatment of research participants and reliable data in clinical research.
- Research staff must adhere to procedures outlined in the research protocol, which must be approved by the Institutional Review Board before the study begins.
- The research protocol provides a plan for crucial aspects of the proposed research and is required by Good Clinical Practice guidelines and Title 21 Part 312 of the Code of Federal Regulations.
- Protocol amendments must be approved by the IRB before implementation and may require submission to the FDA if the study is under an Investigational New Drug application.

- Violations of the research protocol by study staff must be documented and corrected, with additional staff training or protocol amendments as needed to prevent repeated violations.

Record Keeping in Trials

Chapter Eight

Thorough and accurate documentation is an essential element of conducting a successful clinical study. Documentation serves as evidence of the conduct of the study and provides a means to verify the integrity of the data collected. Proper documentation allows the study team to track the progress of the study, identify problems or discrepancies, and take appropriate action to address them. Additionally, documentation is required to comply with regulations and guidelines governing clinical research, such as Good Clinical Practice (GCP) guidelines.

Documentation Requirements in GCP and Federal Regulations

In Good Clinical Practice (GCP) guidelines, essential documents are defined as documents that allow for the evaluation of the conduct of a clinical trial and the quality of the data produced. These documents are crucial to demonstrate compliance with GCP guidelines and applicable regulations, and can be audited or inspected by quality assurance monitors or regulatory authorities to ensure the validity of the study and integrity of the data.

ICH GCP E6 Section 8 outlines the minimum essential documents that must be maintained for every clinical study. These documents are classified according to the stage of the study at which they are created, and should be maintained by both the site and sponsor. The location of these essential documents should be recorded by the sponsor and investigator/institution, including source documents, and may be stored in multiple locations depending on whether they are stored with regulatory files or participant documents. Additional documents may also be developed and maintained by the sponsor or their representatives. Proper documentation is essential to ensure the success of a clinical study and to meet regulatory requirements.

Before the study begins

Before a clinical study begins, certain essential documents must be created and maintained at study sites. These documents allow for the evaluation of the trial's conduct and data quality, and serve to demonstrate compliance with Good Clinical

Practice (GCP) guidelines and regulatory requirements. The list of essential documents, as outlined in ICH GCP E6 Section 8, includes:

1. Signed protocol and amendments, if applicable.
2. IRB-approved Informed Consent Form and other written information given to prospective study participants.
3. Sample case report forms.
4. Participant recruitment advertisements, if any.
5. Documentation confirming IRB compliance and necessary approvals.
6. Decoding procedures for blinded trials, if applicable.
7. Documentation of study personnel qualifications.
8. Documentation of financial agreements and other arrangements between involved parties.
9. Insurance statement, if required, to document compensation for trial-related injury.
10. Instructions for handling, dispensing, and tracking the investigational product, if applicable.
11. Investigator's Brochure, if applicable.
12. Evidence of regulatory authority approval of the protocol and supporting documentation, if required.
13. Evidence of facility approval or certification for medical or laboratory tests.
14. Normal value(s)/ range(s) for medical, laboratory, and/or technical procedures and tests included in the protocol.
15. Reports of site initiation and qualification visits by quality assurance monitors.

These essential documents may be audited or inspected by quality assurance monitors or regulatory authorities to confirm the validity of the study and the integrity of the collected data.

While the study is in progress

During the course of a clinical study, certain essential documents should be added to the study file to ensure proper documentation. These documents, as outlined in ICH GCP E6 Section 8, include:

1. Amendments to the protocol and changes to case report forms (CRFs), informed consent forms, investigator's brochure, and recruitment materials.
2. Documentation of the approval of these amendments by the Institutional Review Board (IRB) and regulatory authorities if required.

3. Copies of all reports sent to the IRB and regulatory authorities, including interim and annual reports.
4. Signed informed consent forms from study participants.
5. Completed CRFs and documentation of any corrections made.
6. Documentation of investigational products and trial-related materials shipment.
7. Relevant communications, such as letters and meeting notes, that document agreements or discussions about protocol violations, adverse events, safety information notifications, and study administration and conduct.
8. Relevant communications other than site visits, such as letters and meeting notes.
9. Reports of interim visits by quality assurance monitors.
10. Curriculum vitae for new investigators and sub-investigators.
11. Source documents.
12. Participant screening log, enrollment log, and identification code list.
13. Documentation that investigational drugs have been handled and accounted for as required by the protocol.
14. Records of location and identification of retained tissue samples, if any.
15. Staff signature log, documenting signatures and initials of all persons authorized to make entries and/or corrections to CRFs.
16. Updates to investigators' and study staff's curriculum vitae (CV), licenses, and certifications.

After the study is completed or terminated

After a study is completed or terminated, it is important to include the following essential documents in the study file:

1. Documentation that investigational drugs were handled, accounted for, and disposed of as required by the study protocol.
2. A list of all participants who were enrolled in the study at the site (completed subject identification code list).
3. Reports of closeout visits by quality assurance monitors.
4. Final reports submitted to Institutional Review Boards and regulatory authorities.
5. If applicable, a clinical study report that documents the study's results.

Federal regulations mandate certain documentation requirements for investigators, as outlined in 21 CFR 312.62. These requirements include:

1. Keeping complete and accurate records of the disposition of investigational drugs.
2. Maintaining detailed case histories for all participants in studies involving investigational products.
3. Holding onto records for a minimum of two years after the date that the FDA approves a marketing application for the drug for the specific indication it was investigated for, or two years after the study has been terminated and the FDA has been informed.
4. All studies sponsored by the NIH must retain records for at least three years following the conclusion of the study, according to NIH policy. This requirement applies to all types of research, such as studies involving investigational drugs, behavioral studies, and survey-based studies. Longer retention times may be required based on regulations or local institutional policies.

Examples of Other Sponsor-Required Documents

Apart from the necessary documents stated in the GCP guideline, additional documentation may be necessary as required by the sponsor for clinical trials. The following are some examples of such documentation that may be required.

1. Certificate of Confidentiality
    a. A Certificate of Confidentiality is an extra measure of safeguarding the confidentiality of individuals participating in studies related to drug and alcohol use.
2. Quality Assurance Documents

    a. The Research Site Initiation Activation Form that confirms the readiness of a research site to begin enrolling participants in the study.
    b. Site visit logs to document visits to the research site by quality assurance monitors and other personnel.
3. Training Documents
    a. A plan for training and verification of staff compliance with the plan, including a form for documenting the training for each staff member.
    b. Records of required assessments as per the study training plan.
    c. Records of training specific to the study.
    d. Relevant certifications for clinical staff responsible for implementing a study intervention.

4. Procedures or Therapy Documents
    a. Studies often necessitate distinct essential documents from those mandated by the GCP guidelines, for example, those that are part of the protocol or study. These documents might comprise of lab reports, x-rays, pathology reports, EKGs, or other treatments and procedure reports, and other documents associated with the study or study follow-up.
5. Source Documents
    a. Original records, data, or documents created during a clinical study, which pertain to the participant's medical treatment and history and from which study data are derived, are known as source documents. According to GCP guidelines, source documents are one type of essential document that is required. The aim of source documents, as stated in GCP 8.3.13, is to:

        i. Confirm the existence of study participants.
        ii. Establish the validity of the study data collected.

    b. Any record that contains information, an observation, or data generated that is pertinent to a study is a source document. As a result, a scrap of paper, a Post-It® note, or an electronic message may be a source document if it is the initial form on which relevant information about a study is documented.

    c. Examples of source documents:
        i. Logs of adverse events and concomitant medications
        ii. Reports of diagnostic test results
        iii. Informed Consent Forms signed and dated by participants
        iv. Participant diaries
        v. Appointment calendars
        vi. Progress notes
        vii. Paper case report forms (CRFs) where data is entered directly onto the CRF, rather than being extracted from another source document.
6. Progress Notes
    a. Readily available and retrievable source materials are essential for quality assurance monitoring and auditing by the study sponsor or for inspection by the U.S. Food and Drug Administration (FDA).
    b. The main purpose of progress notes is to document the study-related care and involvement of participants. Both clinical and research staff can

complete these notes, which serve as source documents and may not be entered into the study database or sent to the sponsor.

c. Progress notes are often used on-site to monitor study progress and help to verify data recorded in the case report forms (CRFs). To be effective, progress notes should be concise yet provide sufficient detail to easily understand the participant's study-related activities and the order in which they occurred.
d. Types of progress notes:
    i. Clinical notes that document information related to the participant's experimental treatment during the clinical phases of the study.
    ii. Research notes that document information related to the participant's involvement in the research phases, such as follow-up assessment visits.

7. Case Report Forms (CRF)

    a. According to GCP guidelines, a Case Report Form (CRF) is a document, whether printed, optical, or electronic, that is designed to collect all the necessary information about each subject in a clinical trial that must be reported to the sponsor (ICH GCP 1.11).
    b. It may be a printed document completed by a team member in the clinic, or an electronic document sent directly from a laboratory to the data management center.
    c. The purpose of CRFs is to collect study data in a standardized format for entry into a computerized database and analysis, which is essential to evaluate the study outcomes.
    d. CRFs can be considered as source documents only if the data entered on the CRF are not extracted from other source documents, such as progress notes.

Documenting the Use of Investigational Drugs

Investigators are mandated by 21 CFR 312.62 to keep thorough records of investigational drug disposition, which should include dates, quantities, and usage by study participants. Furthermore, the investigator is required to maintain records of receipt of the drug.

To understand the drug disposition accountability process, the following equation may be useful:

AMOUNT OF DRUG RECEIVED - AMOUNT USED(i.e. amount ingested + amount lost or not returned) = AMOUNT OF DRUG ON HAND

While the equation appears straightforward, it can be challenging to maintain an accurate record of the disposition of an investigational drug in reality. Investigators must keep track of every unit of the investigational product, such as tablets, capsules, and inhalers. Accounting for each unit of an investigational product involves several complex steps.

To document the "amount of drug received" accurately, the following information must be accounted for:

- The total quantity of capsules, tablets, or other forms of dosage for every strength (e.g., 5mg, 10mg).
- Multiple lot numbers, if applicable.
- The type of packaging that is used to deliver the medication, such as bulk supply or individual kits.

The documentation of the "amount of drug used" should include the following:

- The quantity of medication consumed by each individual participant.
- The total quantity of medication utilized by all the study participants.
- The quantity of medication returned by the participants, which remained unused.
- The quantity of medication that was wasted due to reasons such as loss or accidental disposal.

Regular inventory checks are necessary to verify the "amount of drug on hand," and any inconsistencies must be recorded. It is important to establish a well-planned protocol or standard operating procedure at the start of the study to document the disposition of the investigational product at each site. This protocol must be consistently followed throughout the study, and if necessary, revised to ensure complete accountability. The investigator's documentation of drug disposition must match the information provided to the sponsor.

Chapter Eight Resources

Summary of Key Points:

- Clinical studies require documentation for every aspect to obtain useful data and demonstrate compliance with GCP standards and applicable regulations.
- The GCP guidelines identify essential documents that must be maintained for every clinical study, classified according to when they are normally created.
- Federal regulations require investigators to retain records for two years after FDA approval of the investigational drug or two years after the study is discontinued and FDA is notified.
- Sponsors may require additional documentation beyond the GCP-specified essential documents.
- Source documents are original documents created during a clinical study that are used to obtain study data and document the existence of study participants.
- Progress notes document participant involvement in the study and care received, monitor study progress, and support data recorded in CRFs.
- The purpose of CRFs is to gather standardized study data in a format that can be entered into a computerized database and analyzed.
- CRFs must record all necessary information for data analyses used to evaluate study outcomes.

Research Misconduct and How It’s Dealt With

Chapter Nine

What is Research Misconduct?

Misconduct in research became a public concern in the early 1980s due to reports of serious misbehavior by researchers. Such misbehaviors included a researcher republishing dozens of articles under his name, which had previously been published by others, and falsifying or making up research results. Unfortunately, research institutions sometimes ignored or covered up these problems instead of addressing them.

Eventually, Congress mandated that federal agencies and research institutions create policies on research misconduct. The U.S. Public Health Service responded by establishing regulations for addressing research misconduct (42 CFR 50 Subpart A). These regulations have three primary objectives: defining research misconduct, establishing procedures for reporting and investigating research misconduct, and safeguarding both those who report alleged research misconduct and those accused of research misconduct.

This module will discuss how federal policy defines research misconduct and provide an overview of the procedures developed by the U.S. Public Health Service (PHS) for responding to allegations of misconduct in PHS-supported research.

According to federal regulations, research misconduct is defined as "fabrication, falsification, plagiarism, or other practices that significantly deviate from those commonly accepted within the scientific community for proposing, conducting, or reporting research." Fabrication involves inventing data or results and then recording or reporting them. Falsification involves changing research materials, equipment, or procedures or altering or omitting data or results so that the research record does not accurately reflect the research findings. Plagiarism involves using another person’s ideas, processes, results, or words without giving appropriate credit.

It is important to note that research misconduct does not include honest error or differences of opinion. Moreover, the federal policy on research misconduct does not apply to authorship disputes unless they involve plagiarism. It should also be noted that noncompliance with policies and procedures for the protection of human research subjects, while reportable to an Institutional Review Board (IRB), is not considered to be research misconduct under the federal definition. This module provides an overview of

the processes established by the U.S. Public Health Service (PHS) for responding to allegations of misconduct in PHS-supported research and how federal policy defines research misconduct.

The federal policy on research misconduct is applicable to all proposals submitted to federal agencies for research funding and all research that is federally funded. Some research institutions and universities go beyond the federal policy and apply it to all research, regardless of its funding source. Furthermore, these institutions have extended the definition of research misconduct beyond the federal standards to include other forms of inappropriate practices. Researchers are required to be familiar with both their institutional policies and the federal policy on research misconduct.

Identifying Research Misconduct

Which federal agency is responsible for investigating alleged research misconduct?

The Department of Health and Human Services' Office of Research Integrity (ORI) is responsible for promoting research integrity in the U.S. Public Health Service. ORI oversees investigations of allegations of research misconduct and renders final decisions on findings of research misconduct.

ORI offers technical assistance to institutions that are responding to research misconduct allegations through its Rapid Response Technical Assistance Program. Researchers can also hold informal discussions with ORI about research misconduct allegations or the handling of research misconduct cases.

During the investigation of a research misconduct allegation, ORI maintains records that are exempt from disclosure under the Freedom of Information Act to the extent permitted by law and regulation.

Distinguishing Research Misconduct from Other Types of Misconduct

Research misconduct involves actions that compromise the integrity and honesty of the research record. This sets it apart from other inappropriate behaviors that may occur in research settings, such as financial conflicts of interest, misuse of grant funds, human subject protections violations, sexual harassment, and discrimination. While these

actions are also taken seriously, they are not considered research misconduct because they do not alter the integrity of the research record.

The term fraud has commonly been used to describe dishonesty in research; however, this term more accurately describes illegal or deceptive financial practices. The term research misconduct is more suitable for behavior that undermines the integrity of the research record through fabrication, falsification, or plagiarism.

Investigating Allegations of Research Misconduct

The investigation of allegations of research misconduct is the responsibility of researchers and research institutions according to federal policy on research misconduct. This is in line with the belief held by most researchers that their profession should be self-regulated. Thus, both individual researchers and research institutions have a role to play in ensuring the integrity of research.

Research institutions that receive federal funding are required to create an environment that discourages all forms of research misconduct. They are expected to have procedures in place for receiving and investigating reports of research misconduct. They must inform scientific and administrative staff of these procedures and stress the importance of complying with them. In addition, institutions must take prompt and appropriate action when research misconduct is suspected or alleged. It is their responsibility to investigate and determine if research misconduct has taken place. Institutions must also report both the initiation and the results of formal investigations (not initial inquiries) into allegations of research misconduct to the Office of Research Integrity. Furthermore, they must file an Annual Report on Possible Research Misconduct with the designated federal agency.

According to federal policy on research misconduct, the research profession is expected to regulate itself. For this to work, all members of the profession need to participate conscientiously. Individual researchers are therefore expected to:

1. Adhere to high standards of integrity in all research activities.

2. Take responsibility for their actions.

3. Treat misconduct or suspected misconduct with gravity.

4. Report instances of apparent misconduct by other researchers.

5. Maintain confidentiality of relevant information during investigations of alleged misconduct.

Responding to Allegations of Research Misconduct

Federal policy places the responsibility of reporting and investigating alleged research misconduct mainly on researchers and research institutions. The specific requirements for research institutions when responding to such allegations are outlined in 42 CFR Part 50 Subpart A.

There are three stages involved in responding to an allegation of research misconduct.

INQUIRY

The purpose of the inquiry is to examine the details of the accusation and determine whether a formal investigation is necessary. The inquiry must be completed within 60 calendar days of its initiation, except under extraordinary circumstances. The accused individuals must be notified of the accusation and the inquiry. A written report must be produced at the end of the inquiry that outlines the evidence reviewed and the conclusions drawn. The accused person(s) must receive a copy of the inquiry report.

INVESTIGATION

If the inquiry establishes a sufficient basis, an investigation should commence within 30 days of the inquiry's conclusion. The decision to begin the investigation must be communicated in writing to the Director of the Office of Research Integrity (ORI) by the start of the investigation.

Typically, the investigation will involve reviewing all relevant documents such as research data, proposals, publications, correspondence, and telephone records. Interviews with all whistleblowers, the accused, and anyone with pertinent information about the allegation will also be conducted. The investigation's findings should be documented in a report, which should be made available for review and feedback by all whistleblowers and accused parties.

For research funded or supported by the National Institutes of Health (NIH), the final report must be submitted to ORI, the principal investigator, the sponsor, and NIH. In most cases, the investigation should be completed within 120 days of its commencement. If the institution is unable to finish the investigation within this time frame, it must submit a written request to ORI for an extension. This request must include the reason for the delay, progress of the investigation so far, and an estimated completion date for the investigation and final report.

ADJUDICATION

When an investigation finds that an allegation of research misconduct is valid, the research institution may impose appropriate penalties. Moreover, the Office of Research Integrity (ORI) may also levy penalties on individuals or institutions involved in the misconduct. During an inquiry or investigation into a research misconduct allegation, the research institution must immediately notify the ORI if specific circumstances are discovered.

Safeguards for Informants and Accused Persons

To ensure fairness and timeliness in responding to allegations of research misconduct, it is important to recognize that such accusations can have a profound effect on the informant, the accused party, and the institution involved. To maintain the integrity of the process, it is necessary to have procedures in place to safeguard original documents, computers, biological specimens, laboratory notebooks, research, and financial records, and any other relevant items that may be at risk of alteration, loss, or destruction.

Furthermore, it is important to establish safeguards to ensure the protection of all parties involved in an allegation of research misconduct.

A whistleblower, or informant, is someone who alleges that a research institution or one of its members has engaged in research misconduct, or has failed to respond adequately to such an allegation. This can include both employees and non-employees of the institution. The role of whistleblowers is critical in safeguarding the integrity of research. It is important that those who report apparent research misconduct in good faith are able to do so confidentially, without fear of retaliation or any form of retribution.

According to federal policy, institutions are obligated to provide certain protections to informants, including safeguarding their privacy to the fullest extent possible, although

anonymous reporting is not permitted. Informants must also be protected from retaliation and be ensured fair and unbiased procedures for investigating and resolving allegations of research misconduct. Additionally, institutions must take care to protect the positions and reputations of informants by acting diligently to address the allegations.

It is not permissible for research institutions or individual researchers to punish individuals who report allegations of research misconduct in good faith. Informants must be protected regardless of whether the allegations are proven, as they are crucial to ensuring the integrity of professional self-regulation.

The majority of accusations of research misconduct do not result in findings of wrongdoing. Therefore, individuals who are accused of misconduct should not face disciplinary action or be prevented from continuing their research without sufficient cause, simply based on the filing of an allegation.

Additional protections for individuals accused of research misconduct include receiving written notification in a timely manner about the allegations against them, a comprehensive description of all allegations, access to the data and evidence supporting the allegations, and the opportunity to respond to the allegations, supporting evidence, and any proposed findings of research misconduct. Confidentiality is also provided to the maximum extent possible.

Those chosen to investigate allegations of research misconduct must possess relevant expertise and have no unaddressed conflicts of interest to ensure objectivity.

In responding to an allegation of research misconduct, it is important to establish reasonable timeframes for the process. Extensions may be granted when necessary.

The protection of confidentiality should be upheld to the extent possible during investigations of research misconduct, including the identities of the individuals involved. However, the accused party must be informed of the informant's identity. In the event of alleged misconduct in a clinical trial that poses a risk to participants' safety, it must be reported immediately to the trial's principal investigator, the sponsoring federal agency, and the Office of Research Integrity (ORI). While the identity of the accused

person(s) should remain confidential, appropriate measures must be taken to ensure the safety of trial participants.

Possible Penalties for Research Misconduct

Researchers who are found guilty of research misconduct may face penalties such as termination of employment or supervision of future research activities by their respective institutions. In cases where a finding of research misconduct is upheld by a grantee institution working on an NIH-funded research project, the grantee must evaluate the impact of the finding on the individual's ability to continue working on the project. Furthermore, the grantee must seek approval from the sponsor and NIH for any changes in principal investigators or other key personnel involved in the research project.

Penalties for research misconduct may be imposed by the Office of Research Integrity (ORI), and the severity of the penalty is based on the seriousness of the misconduct. In determining the appropriate penalty, the ORI may consider several factors, including whether the misconduct was committed knowingly, intentionally, or recklessly, whether it was an isolated incident or part of a pattern, and the extent to which it impacted the research record, research subjects, other researchers, institutions, or public welfare.

When a finding of research misconduct is upheld, the Office of Research Integrity (ORI) has the authority to impose various penalties, which may comprise correction of the research record, issuance of letters of reprimand, suspension or termination of a research grant, and suspension or debarment from receiving federal funds.

The individuals subject to administrative actions by ORI (or the FDA, which maintains separate bulletin boards for debarred and disqualified investigators) will have their names publicly disclosed. In cases where the ORI suspects that research misconduct may have involved criminal or civil fraud, the matter will be promptly referred to an investigative body such as the Department of Justice or the Office of the Inspector General, Department of Health and Human Services.

The implementation of ICH GCP came about as a result of public outrage over research misconduct that had taken place over time. Adhering to the ICH GCP guideline helps prevent fraud and misconduct, which can be considered a type of non-compliance with ICH GCP.

Chapter Nine Resources

Summary of Key Points:

- Research misconduct involves fabrication, falsification, or plagiarism in research proposals, performance, review, or reporting of results, but not honest errors or authorship disputes unless they involve plagiarism, according to federal policy.
- This policy applies to all federally funded research and proposals submitted to federal agencies for funding.
- The Office of Research Integrity (ORI) is responsible for overseeing investigations of allegations of research misconduct within the U.S. Public Health Service.
- Researchers and research institutions are primarily responsible for reporting and investigating allegations of research misconduct.
- An allegation of research misconduct is usually responded to by an inquiry to assess the facts, followed by an investigation if the inquiry provides a sufficient basis, and finally an adjudication with appropriate penalties if the allegation is found to be valid.
- Penalties for research misconduct can include termination of employment, suspension or termination of a research grant, and suspension or debarment from receiving federal funds.

Clinical Research Roles and Responsibilities

Chapter Ten

Conducting a clinical study involves the participation of various individuals and groups. Good Clinical Practice (GCP) guidelines define the central roles of the Sponsor and Principal Investigator, while additional roles and responsibilities are assigned to other individuals and groups, whose reference may vary across different research networks.

Responsibilities by Role

The central roles in conducting a clinical study include the Sponsor, Principal Investigator, and other roles such as Research Site Staff.

Responsibilities of a Sponsor:

Monitoring:

All NIH-supported Phase III clinical trials conducted at multiple centers must have a Data and Safety Monitoring Board (DSMB) which is independent. This requirement is applicable to both behavioral and drug therapy studies. Members of the DSMB include experts in research ethics, biostatistics, clinical trial design, disease area, and treatment. They are appointed by and report to the sponsor.

The DSMB's role is to protect participant safety by reviewing outcome and safety data as it becomes available, proposing appropriate analyses, and being familiar with the study. Additionally, they ensure study integrity by reviewing data on issues such as participant enrollment, data quality, site visits, losses to follow-up, and adherence to the study protocol. The DSMBs also monitor adverse events and recommend changes in the protocol or operation of the study if necessary. The monitoring function is critical for multicenter research studies and goes beyond the oversight typically provided by the IRB.

Quality Assurance and Quality Control:

In accordance with ICH GCP 5.1, the responsibility for establishing and maintaining quality assurance and quality control systems to ensure that clinical studies adhere to the protocol, GCP, and regulatory requirements lies with the Sponsor.

Medical Expertise:

Designating qualified medical personnel to provide guidance on medical issues related to the clinical trial is the responsibility of the Sponsor, according to the Medical Expertise (ICH GCP 5.3) guideline.

Study Design and Management:

The Sponsor is accountable for appointing competent personnel to manage and oversee every aspect of the study, from designing the protocol to preparing study reports. This includes supervising the study's overall conduct, managing and verifying the study data, ensuring human participants' safety and rights, monitoring the study's performance, planning and conducting the statistical analyses.

Transfer of Trial-Related Obligations:

To delegate its trial-related responsibilities, the Sponsor can transfer some or all of its duties to a Contract Research Organization (CRO). Nevertheless, the accountability for the quality and accuracy of the trial data always remains with the Sponsor. The specific trial-related responsibilities that are transferred to the CRO should be documented in writing.

Responsibilities of a Principal Investigator:

Although a Lead Investigator is typically responsible for the entire trial, often the Principal Investigator (PI) at the main research site serves in this capacity and oversees the study at that particular site. In multicenter trials, there are several research sites, each with its own Principal Investigator responsible for oversight and staff engaged in study conduct.

The Principal Investigator (PI) has ultimate oversight responsibility for a clinical study even if certain tasks are delegated to other research staff at the site. The PI's responsibilities include documenting the delegation of study responsibilities to qualified and well-trained staff, supervising study performance and the work of site staff, and ensuring the safety and well-being of participants, as well as adherence to the study protocol and GCP. Additionally, the PI is responsible for preparing a communication plan for all study staff and overseeing Investigational product accountability.

It is important to mention that the PI is required to sign the protocol signature page in their capacity. Moreover, if the study is carried out under an Investigational New Drug (IND) application, the PI must sign Form FDA 1572 as well.

Qualifications and Experience:

To meet the requirements of ICH GCP 4.1, the PI should have the necessary education, training, and experience to carry out the study properly. If the study includes an investigational product, the PI should have adequate knowledge about its use as specified in the study protocol. Also, the PI should ensure compliance with GCP and applicable regulatory standards, and maintain a record of qualified personnel to whom significant study-related responsibilities can be delegated.

Medical Care of Study Participants:

It is important that study participants receive adequate medical care for any study-related adverse events and unrelated medical conditions. This care should be overseen by a qualified physician associated with the study, who is responsible for all medical decisions related to the study. If the participant has a primary care physician, they should be notified about the participant's involvement in the study, provided that the participant consents to the disclosure of such information.

Communication with Institutional Review Board:

The PI is assigned to the designated IRB and must adhere to all requirements of the IRB before and during the study. IRB approval must be obtained before commencing the study.

Compliance with the Protocol:

The responsibility of ensuring that the study adheres to the research protocol lies with the PI. The PI should identify, document and report all protocol violations as per the sponsor and IRB requirements. Repeated protocol violations may necessitate amendments to the protocol, procedural changes, or additional training.

Use of Investigational Products:

Responsibility for the investigational product in a study involving it lies with the PI, who must ensure its use is in compliance with the study protocol and applicable regulations. Moreover, the PI must maintain accountability of the investigational product.
In clinical investigations where a controlled study drug is used, the PI may be obligated to have a medical license. Otherwise, qualified medical personnel such as a physician, physician's assistant, nurse practitioner or another licensed medical professional may be responsible for administering and receiving certain drugs, reviewing safety events, and making independent medical decisions.

These delegated responsibilities and the assigned staff are documented in the site's delegation of responsibilities log, and the staff assigned may serve as a sub-investigator. Local regulations and oversight authorities should be consulted on medical license requirements for research involving controlled drugs.

Randomization and Blinding:

The PI is responsible for ensuring compliance with the study's procedures for randomization and blinding, if applicable, in accordance with ICH GCP 4.7.

Informed Consent:

Responsibility for obtaining and documenting informed consent, in compliance with GCP and ethical principles from the Declaration of Helsinki, falls upon the PI as outlined in ICH GCP 4.8.

Records and Reports:

Responsibility for the accuracy, completeness, legibility, and timely reporting of all study data to the sponsor lies with the PI according to ICH GCP 4.9. The PI must submit written reports to the sponsor and the IRB on the study's progress as required at each institution where the study is taking place. Any serious adverse events must be promptly reported to the sponsor, and the PI is obliged to comply with regulatory requirements to report such events to the IRB and regulatory authorities.

Final Study Reports:

According to ICH GCP 4.13, the PI must ensure that all necessary reports are submitted to the sponsor and regulatory authorities upon the completion of the study. In addition, the PI is responsible for providing a summary of the study outcome to the Institutional Review Board. More information about records and reports can be found in the Documentation and Record Keeping module, while the Participant Safety and Adverse Events module provides a detailed discussion of serious adverse events.

Premature Suspension or Termination of Study:

Responsibility for Premature Suspension or Termination of Study, as per ICH GCP 4.12, lies with the PI. In the event of the study being stopped or suspended early, the PI is accountable for ensuring that all study participants are informed promptly, receive appropriate therapy and follow-up, and that all regulatory authorities are duly notified in compliance with relevant requirements.

Responsibilities of Other Roles:

The Protocol Team, convened by the investigator, provides assistance with all aspects of the study's operation. Along with the responsibilities listed for the Principal Investigator, the team typically includes other duties such as Quality Assurance, Training, and Regulatory Affairs, among others.

Quality Assurance:

The responsibilities of the Quality Assurance (QA) staff include:

- Checking the protocol for any inconsistencies and problematic wording that may increase the chances of protocol violations.
- Reviewing the monitoring reports of site visits to ensure that all issues are addressed in a suitable and timely manner, and that they are communicated to the investigative team.
- Conducting site visits on behalf of the Sponsor, as necessary.

Regulatory Affairs:

The responsibility of the Regulatory Affairs staff includes:

Composing the study's informed consent documents.
Submitting the protocol, consent documents, and Institutional Review Board (IRB) documents to the lead node's IRB and making necessary changes as required by the IRB.
Assisting participating research sites in preparing their IRB submissions by distributing the IRB-approved protocol, consent documents, and Institutional Review Board (IRB) documents.
Creating and distributing a checklist of necessary items that participating sites must possess.
Providing regulatory assistance to the study sites as needed.
This responsibility persists throughout the duration of the trial, such as the submission of a Protocol Amendment.

Responsibilities of the Research Site Staff:

Research Coordinator/Assistant:

The Research Coordinator/Assistant, supervised by the PI at the site, may be responsible for various tasks, such as:

- Accurately collecting and reporting study data.
- Promptly reporting any issues related to the study or participants.
- Maintaining regulatory files at the study site.
- Collaborating with the Node Quality Assurance Monitor and data management staff to detect and resolve data and reporting issues.

The responsibilities of the Research Assistant often involve conducting assessments (such as the Addiction Severity Index) and following protocol procedures while interacting with study participants.

Nurses, Pharmacists, Counselors, Supervisors, and Other Staff:

The responsibilities of nurses, pharmacists, and other staff include executing study procedures outlined in the protocol, such as receiving and dispensing medications, performing physical examinations, and administering behavioral interventions. Additionally, they are accountable for assessing and notifying relevant staff of any adverse events.

Chapter Ten Resources

Summary of Key Points:

- Good Clinical Practice (GCP) guidelines define the roles and responsibilities of the Sponsor and Principal Investigator (PI) in clinical studies.
- The Sponsor is responsible for ensuring the quality and validity of the trial data and can delegate some duties to a partner organization or a contract research organization (CRO).
- The PI is responsible for overseeing the conduct of the clinical study at the research site.
- The PI's responsibility persists even if certain tasks are assigned to other staff members at the site.

Recruiting and Retaining Research Participants

Chapter Eleven

The Importance of Recruitment and Retention

Recruiting and retaining participants are crucial aspects of a clinical study as they enable researchers to answer the research question at hand. It is essential for researchers to recruit an adequate number of suitable participants and keep as many of them as possible throughout the study's specified time period.

Clinical studies rely on recruitment and retention of participants to achieve their objective of answering research questions. However, studies often make overly optimistic projections for recruitment and retention, which can lead to failure if not met. In such cases, participants may have been put at risk for no purpose, and the research question may remain unanswered. Therefore, successful recruitment and retention are crucial for the success of any clinical study.

Achieving successful recruitment and retention requires careful planning, adequate resources, monitoring, and prompt resolution of any issues that may arise. Furthermore, any recruitment and retention strategies, including advertising materials, must be approved by the Institutional Review Board (IRB) before implementation.

Recruiting and retaining participants in studies is a challenging task that requires significant time and effort from clinicians and researchers alike. This module provides guidance on the issues that need to be considered when recruiting and retaining participants for studies.

Recruitment

Recruiting participants for a study involves two primary components: identifying a suitable population to address the research inquiry and recruiting them in an ethical manner. Consideration of various issues is necessary when defining the participant population for a clinical study.

The appropriate participant population for a clinical study is often defined by the **study's purpose**. For instance, a study aimed at testing an intervention for pregnant women with gestational hypertension, runaway teenage girls involved in the criminal justice system, military veterans who use tobacco products, or another specific subgroup will define the appropriate participant population for the study.

The relevance of a clinical study's findings to individuals who were not part of the study, but share similar characteristics as the participants, is crucial. This is known as **generalizability**. Sufficient number of participants are needed to ensure that the results of the study can be extended to the general population, which could potentially benefit from the research.

The current system of human research protections is based on the three key principles of the 1979 **Belmont Report**, which include respect for persons, beneficence, and justice. One of these principles is the principle of justice, which requires that participants be selected in a fair manner. In selecting participants, researchers must strive to allocate the risks and benefits of participation fairly and without bias across the population.

It is important to select participants based on their relevance to the problem being studied, rather than their availability, compromised position, or vulnerability. Additionally, research should not involve groups of people who are unlikely to benefit from subsequent applications of the research, unless there is a clear justification for doing so. For example, selecting only persons on welfare, institutionalized persons, or members of a specific racial or ethnic group as study participants would be unethical unless the intervention being studied was intended to directly benefit that group.

To ensure the meaningfulness of research findings and equal access to benefits, it is important to include adequate representation of women and minorities in the study population, especially for diseases, disorders, and conditions that disproportionately affect these groups. The National Institutes of Health has mandated since 1994 that researchers provide a clear and compelling justification for conducting studies without adequate representation of women and minorities.

Certain groups of individuals, such as children, prisoners, economically disadvantaged or educationally disadvantaged persons, are considered to be more susceptible to being coerced into participating in research. For this reason, participants from vulnerable populations should only be enrolled in studies that are directly relevant to their circumstances. For instance, pregnant women should only participate in studies that are

relevant to pregnancy, such as investigating the effectiveness of different treatment strategies for pregnant women with substance use disorders.

When vulnerable participants are being recruited for a study, additional safeguards must be included in the protocol to ensure that their rights and welfare are protected. However, vulnerable populations should not be overly protected to the extent that they are excluded from participating in research.

The study's eligibility criteria define who can participate and who cannot, and they must be outlined in the study protocol. In reviewing potential participants, both inclusion and exclusion criteria should be carefully assessed.

Inclusion criteria determine the characteristics necessary for a potential participant to be eligible for the study. Conversely, exclusion criteria identify the characteristics that would prevent someone from enrolling in the study. Meeting all the inclusion criteria is generally required for eligibility, while meeting any exclusion criteria would result in ineligibility.

The criteria for inclusion and exclusion must be reasonable and relevant to the study's objectives. Any individual or group should not be excluded without a valid reason, and no one should be included unless they can benefit from the research. If the admission criteria are too strict, it may be difficult to recruit enough participants, and easing the criteria may positively impact recruitment. Conversely, overly broad criteria may make it difficult to draw meaningful conclusions from the study and increase safety concerns.

Recruitment Strategies

The following are key elements to consider when developing a successful recruitment strategy:

1. Ensure that inclusion and exclusion criteria are not unnecessarily restrictive.
2. Determine fair compensation for participants that is not coercive.
3. Develop a recruitment plan during the protocol planning phase.
4. Allocate sufficient budget for recruitment expenses, including advertising, staff time, and start-up training.
5. Create a profile of prospective participants, considering what might motivate them to participate, where they obtain information, and where they live, work,

shop, and play. Use this information to identify appropriate media outlets for recruitment advertisements and potential referral sources.
6. Review recruitment rates, dropout rates, and screening success rates from past studies to build on successful strategies and learn from past failures.
7. Choose appropriate staff to conduct recruitment and track the number of participants enrolled per recruiter per site.
8. Monitor recruitment progress and intervene quickly if necessary to modify recruitment techniques.
9. Identify and address barriers to recruitment.

It is important to use these elements in conjunction with each other for a coordinated and effective recruitment strategy.

Here are some specific strategies for recruiting participants into clinical studies:

1. Respond to interested prospects promptly. A delayed response from study staff reduces the likelihood of enrollment.
2. Build relationships with potential referral sources such as clinic staff, local healthcare providers, and other relevant individuals. Send targeted mailings to selected healthcare providers.
3. Provide presentations to clinic staff about the study and give regular updates on its progress.
4. Participate in various forums such as health fairs, support groups, and public speaking engagements. Also, consider television and radio interviews.
5. Request public service announcements on radio and television to increase awareness of the study.

Overall, a combination of these strategies used in a coordinated manner can be effective in recruiting participants into clinical studies.

When recruiting individuals with substance use disorder for clinical studies, it is essential to ensure that potential participants are not exploited. To achieve this, guidelines have been set forth by the National Advisory Council on Alcohol Abuse and Alcoholism, which are applicable to studies involving drugs other than alcohol. The guidelines stress that:

- Recruiting people with substance use disorder solely because they are readily available, socioeconomically disadvantaged, or have limited understanding of the research must be avoided.
- The target population for the study must be suitable with respect to age, gender, family or genetic background, past alcohol or drug use, overall physical and psychological health, and if relevant, alcoholism recovery status.

There are generally three ways to recruit participants for clinical studies. One is to ask clients who are already receiving treatment at a research site to consider enrolling in appropriate studies. Another is to receive referrals from other healthcare providers for potential study participants. The third way is to place advertisements in newspapers, flyers, radio, or television, or to use websites to recruit and screen participants. Using websites can be especially useful for recruiting participants for studies related to socially embarrassing diseases or conditions.

Before any recruitment for a study can begin, all recruitment strategies must be approved by the Institutional Review Board (IRB) assigned to the study. It's important to note that certain rules apply when participants are recruited through advertising, which will be discussed in the next section.

Advertising for Study Participants

The materials used to inform and recruit potential study participants, such as advertisements, fliers, and brochures, are considered a part of the informed consent process. Thus, they need to be evaluated and sanctioned by the designated IRB.

It is essential to note that participant recruitment cannot commence until the IRB approves the protocol, informed consent documents, and proposed recruitment and advertising materials. The IRB conducts a comprehensive review of the advertising materials, including their wording, presentation, and intended mode of communication (such as print, radio, or television), to ensure that none of the materials are misleading or coercive in any way.

In what ways could advertising aimed at recruiting study participants be considered misleading? The following are examples of statements or actions that could be seen as misleading:

1. Stating that a study involves no invasive procedures when, in fact, participants will need to have blood drawn.
2. Creating the impression of a positive outcome by:
    1. Using terms such as "new treatment," "new medication," or "new drug" without clarifying that the treatment is investigational.
    2. Implied that the drug or treatment is equal or superior to any other available drug or treatment.
    3. Offering "free medical treatment" instead of explaining that participants will not be charged for taking part in the study.
    4. Making an assertion like "We will cure you in six easy steps."

Retention

Why is it important to maintain study participants throughout the duration of a study? Although recruiting an adequate number of participants is crucial, it is not enough to ensure the success of a study. Retaining participants until the end of the study is equally important, as it ensures that their data can be included in the final analysis.

If too many participants drop out before the study is complete, investigators may not obtain enough data to answer the research question they posed when initiating the study. Additionally, retaining enrolled participants is more cost-effective than recruiting new ones, as managing and retaining them requires fewer resources.

Retention refers to ensuring that participants complete study procedures at the required intervals, respond to questionnaires or interviewers' questions, participate in any other required activities, and attend follow-up visits as required by the study protocol.

Retention Strategies

A successful retention strategy involves treating the participant respectfully and being mindful of their time, as well as addressing any potential obstacles to retention. It is also important to include retention strategies in the study budget and to identify and resolve problems promptly. When developing a retention strategy, the following factors should be taken into account.

Retaining participants in a study starts with their first visit, especially during the informed consent process, where it is crucial to make sure they understand the study procedures, their importance, and the time commitment required. To facilitate participant retention, templates or electronic CRFs may be used to gather contact information, also known as locator forms. This information can include the participant's address, phone number, and contact details of friends and family who can be contacted with the participant's consent. This information will assist in locating the participant if they miss a visit.

Retention strategies should be developed early on during the study design phase, rather than waiting until the last participant is enrolled. It may be necessary to review the participant's contact information with them at each visit, particularly if the study population includes individuals with substance use disorder who often change their home address or job. It is important to maintain up-to-date contact information for all participants throughout the study to facilitate ongoing communication and retention efforts.

Responsibility for retention should be shared by everyone involved in the clinical study. It is important that all staff members in the clinic receive proper training to appreciate the significance of maintaining accurate and up-to-date contact details for all study participants. Participants may mention a change in their personal circumstances at any point, which should be noted in their records and communicated to the entire research team.

The following are some specific strategies that can be used to retain participants in a clinical study:

- Emphasize the importance of compliance throughout the study, starting from the informed consent process.
- Build a good rapport with participants to encourage their commitment to the study.
- If a participant is missing, use their contact information to locate them, such as by calling their home or contacts or visiting their home (if allowed).
- Explore public information sources, like government agencies, to locate participants.
- Modify the study protocol to make it easier for participants to complete assessments or procedures they find unpleasant.

- Conduct regular teleconferences with project staff to brainstorm new retention strategies.
- Send reminder notes before scheduling the next assessment or visit.
- Conduct research interviews at a convenient location for the participant.
- Offer transportation to and from the study site.
- Persistently try to contact participants and document all attempts, while respecting their privacy.

Using Incentives for Study Participation

In order to encourage participation in research studies, incentives such as monetary compensation, free medical care, extra vacation time, food, and lodging may be offered to participants. It is important to note that these incentives are not considered benefits of study participation, but rather inducements to participate.

However, it is possible for any inducement to be coercive or to unduly influence potential participants. For example, those who are struggling financially may be more likely to participate in a study due to the offer of monetary compensation or other rewards, even if it goes against their better judgment.

Due to the potential for coercion, the amount and conditions of any incentives offered to participants must be carefully reviewed and approved by the Institutional Review Board (IRB).

Would it be ethical to provide incentives to individuals with substance use disorder to participate in research? Some researchers are hesitant to offer any incentives for study participation to individuals who are unemployed or economically disadvantaged, out of concern that it might unduly influence them. However, assuming that any form of compensation offered to participants with substance use disorder will serve as an undue influence is unjustified.

When considering the use of incentives to encourage study participation, it is important to take into account three key factors.

The **monetary value** of an incentive should be appropriate and proportional to the level of burden or effort required for participating in the study. It should not be excessive to

the point where it could be considered coercive and influence an individual's decision to participate in the study.

The **timing and method of payment** for incentives should be carefully considered. Credits or rewards should be given progressively as the study progresses, rather than being given as a lump sum at the end of the study. Payment should not be dependent on a participant completing the entire study, but it may be reasonable to offer a bonus for completion. However, the completion bonus should not be so high that it encourages participants to continue in the study when they would otherwise have withdrawn. In some situations, participants who withdraw from the study may be paid at the time they would have completed the study had they not withdrawn. For example, if the study only lasts for a few days, all participants, including those who withdrew, may be paid upon completion.

Forms of payment may include cash, store gift cards, money orders, or check cards. However, some IRBs are cautious about approving cash payments for certain populations, like those with substance use disorder, due to concerns that the payment may be used for drug purchases. Avoiding cash payments can be seen as paternalistic and disrespectful. Some payment options, such as money orders or check cards, may require identification, which could be problematic for populations like those with substance use disorder. Participants should be informed about taxes that may apply to payments exceeding a certain amount.

What to Do when a Participant Leaves a Study

The study protocol ought to outline the guidelines for withdrawal and the steps to take when a participant withdraws voluntarily, exits the study early due to safety concerns, or finishes the study. The protocol must cover the following details:

- The circumstances and methods for withdrawing participants.
- The data to collect (if any) for participants who have withdrawn.
- Whether follow-up is possible for some or all participants who have withdrawn.

Typically, the end-of-study procedures consist of a final interview, referrals, and a follow-up period of specified duration, although there may be other procedures as well.

The final interview, also known as the closing interview, is a crucial step in the study as it is the last chance to gather important data and possibly the last time the research

team interacts with the participant. Additionally, this interview allows for any adverse events that the participant may have experienced during the study to be documented for potential follow-up after the study concludes.

It is the responsibility of the research team to ensure that any participant who leaves the study is provided with necessary referrals to obtain services or help elsewhere, if they desire it.

Follow-up interviews may be necessary after a participant is discharged from the active treatment phase of the study. The study team may inform the participant of this requirement during the closing interview and attempt to schedule the follow-up interview if possible. The participant's locator form should also be reviewed to ensure that all contact information is current.

The majority of trial participants have a positive outlook on their experience and are willing to participate in future studies if given the opportunity. The informed consent process often includes obtaining permission to contact participants for future studies. To avoid wasting this potential resource, it is important to keep participants who have completed a study informed about the study's progress and results, and express gratitude for their participation. These actions may also serve as informal advertising for the study and future research opportunities. A thank-you note or certificate of appreciation could also indirectly encourage participants to participate in future studies.

Chapter Eleven Resources

Summary of Key Points:

- Recruitment and retention are critical to a clinical study's success.
- Successful recruitment and retention strategies require informed planning, adequate resources, careful monitoring, and timely problem identification and resolution.
- Recruitment can begin only after IRB approval of the protocol, informed consent documents, and proposed recruitment and retention strategies.
- Advertisements, fliers, and brochures are part of the informed consent process and require IRB approval.

- Recruitment has two major elements: defining an appropriate participant population and recruiting participants ethically.
- Recruiting an adequate number of participants does not guarantee study success; retaining participants for the study's duration is also essential.
- Rewards like monetary payments or medical care at no cost may be offered to research participants to incentivize participation.
- Such rewards are not benefits but incentives for participation and must be reviewed and approved by the IRB to ensure they are not coercive.

Investigational New Drugs and Clinical Trial Phases

Chapter Twelve

What are Investigational New Drugs?

According to ICH GCP, an **investigational product** is defined as a form of an active ingredient or placebo that is being tested or used as a reference in a clinical trial. This definition covers a marketed product that is being used in a different form or for a new indication that has not been approved.

The term "**investigational new drug**" is defined in the Code of Federal Regulations (CFR) as a drug or biological drug that is used in a clinical investigation. This can include a substance for which approval from the U.S. Food and Drug Administration (FDA) is being sought, such as a drug, vaccine, or other biological product.

Even if a drug has been in use for years, a change in its use, formulation, route of administration, use in patient population where risk would be increased, or packaging can make it "new" and subject to investigation. For instance, a drug that was previously approved for the treatment of high blood pressure may require investigational use if the manufacturer wants to test it for treating anxiety in adults. Throughout study-related documents, an investigational new drug may be referred to as the "study drug," "experimental product," "experimental drug," "new intervention," or similar terms. The CFR Title 21 Part 312 (21 CFR 312) regulates investigational new drugs.

When labeling an investigational new drug, it is required to include a statement that says "Caution: New Drug — Limited by Federal (or United States) law to investigational use." It is important that the labeling is not false or misleading, and does not suggest that the drug is safe or effective for its investigational purpose.

The administration of an investigational new drug must be supervised by the principal investigator or sub-investigator, typically a physician, and only authorized individuals may receive the drug. The use of controlled substances in research must follow regulations set by the U.S. Drug Enforcement Administration (21 CFR 1300-end). When an investigational new drug is considered a controlled substance, the investigator must

take measures to prevent the drug from being stolen or diverted for illegal use. These measures may include storing the drug in a securely locked cabinet or enclosure that has limited access.

To promote or advertise an investigational new drug as safe or effective for its investigational purpose is prohibited for both investigators and sponsors. It is also prohibited to commercially distribute or test-market an investigational new drug. If sufficient data is found to support a marketing application during the investigation, the study should be stopped, and further enrollment should not take place. Unless the drug is being provided for treatment use, charging for an investigational new drug in a clinical trial is not allowed without FDA approval.

Phases of Clinical Trials of Investigational New Drugs

Clinical trials involving investigational new drugs generally consist of four phases: Phase 1, Phase 2, Phase 3, and Phase 4. Additionally, there are Phase 0 or “exploratory” trials, which are small-scale clinical trials (usually with only a few participants) involving subtherapeutic dosing. Although less common than Phases 1-4, Phase 0 trials also exist. Each phase of a clinical trial is designed to gather different information. While the phases are typically conducted sequentially, there may be some overlap between them. Eligibility for participation in a clinical trial's various phases depends on several factors, including age, general health status, the type and stage of the disease, and prior therapies received.

Phase 1 Trials:

Phase 1 trials mark the initial stage of testing an investigational new drug in human subjects, often involving healthy volunteers and sometimes individuals suffering from the targeted disease. Typically, 20 to 80 participants are enrolled in Phase 1 trials. The primary objectives of Phase 1 trials are to assess the safety of the drug in humans, identify any potential side effects, and establish a safe and effective therapeutic dosage range.

Phase 2 Trials:

Phase 2 trials typically involve a larger number of participants than Phase 1 trials, usually several hundred individuals who have the disease or are at high risk of developing it. The objective of Phase 2 trials is to evaluate the effectiveness of the drug in treating or preventing the disease of interest, determine the optimal dose, and identify common short-term side effects and risks associated with the drug.

Phase 3 Trials:

Phase 3 trials are typically carried out when initial results from Phases 1 and 2 indicate that the investigational new drug is both safe and effective. These studies typically involve several hundred to several thousand participants.

The objectives of Phase 3 trials are to:

1. Gather further data on the safety and effectiveness of the drug, to evaluate whether its benefits outweigh any risks.
2. Compare it to other commonly used treatments for the same condition (if available) or compared to a placebo. Such studies can be conducted in a blinded manner.
3. Assess any interactions with other treatments that may be administered concurrently with the investigational new drug.
4. Provide sufficient data to determine the indication for which the drug will be labeled if it is approved for marketing, as well as any limitations on the drug's use that should be stated in the labeling. For instance, if there were insufficient data to demonstrate that a drug can be safely administered to children, the labeling would restrict the drug's use to adults.

Phase 4 Trials:

Following marketing approval, Phase 4 trials are performed to achieve the following objectives:

1. To further assess the short-term safety profile of the drug or treatment.
2. To investigate the efficacy of the drug or treatment in diverse patient populations.
3. To obtain information about the potential long-term adverse effects that may arise from prolonged use of the drug.

Investigational New Drugs Requirements

To conduct clinical trials involving an investigational new drug, the sponsor must submit an Investigational New Drug application (IND) to the FDA. The holder of the IND is considered the sponsor in such studies.

To obtain authorization to conduct a clinical trial involving an investigational new drug, the sponsor must submit an Investigational New Drug application (IND) to the FDA. The IND should contain the following information:

1. The name and contact information of the sponsor and the phase(s) of the proposed trial.
2. A commitment to have an IRB responsible for initial and ongoing review of the trial.
3. The drug's name, active ingredients, dosage, and route of administration.
4. The proposed objectives and duration of the clinical trial(s).
5. A brief description of the plan for investigating the drug, including the rationale for the drug or study, the indication(s) to be studied, the types of clinical trials to be conducted in the first year after the IND submission, the anticipated number of patients, and any serious risks based on animal studies or previous human studies of the drug or related drugs.
6. For most trials, a copy of the investigator's brochure.
7. A protocol for each planned study.
8. The qualifications and identities of all investigators (as demonstrated in a Curriculum Vitae and Form FDA 1572).
9. The criteria for selecting and excluding patients, as well as an estimate of the number of patients to be studied.
10. A summary of previous experience with the drug in animal and human studies, including previous INDs, experience with the drug in other countries, known safety issues, chemistry and manufacturing information, and dependence and misuse potential (if relevant).

Once the FDA receives an IND, it becomes effective after 30 calendar days unless the sponsor receives written permission from the FDA to begin the study before that time or the FDA notifies the sponsor that a clinical hold has been placed on the investigation. Sponsors may request advice on specific IND-related matters from the FDA, and

meetings between the FDA and sponsors can be useful, as long as they are within the limits of FDA resources.

Exemption of IND for Studies of Lawfully Marketed Drugs:
Studies of drugs that are already approved in the market are exempt from IND regulations if they satisfy all
five criteria outlined in 21 CFR 312.2(b)(1). The first four criteria require no explanation. They are as follows:

- The study is not intended to support the approval of a new indication or a significant change in the product's labeling.
- The study is not intended to support a significant change in the product's advertising.
- The study is carried out in compliance with Institutional Review Board (IRB) and informed consent regulations.
- The study will not be used to promote non-approved indications.

The fifth criterion, however, needs to be interpreted.

- The investigation should not involve any factor, such as a route of administration, dosage level, use in a patient population, that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.

It is the responsibility of the investigator to determine whether an IND is required for a study involving a marketed drug. The key question for determining whether such a study is exempt from IND regulation is whether the study “significantly increases the risk” associated with drug use.

If an investigator is confident that a drug study does not require an IND, he or she may not submit an IND application. If the investigator is uncertain about whether an IND is necessary or wants proof of the IND-exempt status of a study, the IND application can be submitted with a request for exemption from IND guidelines, and FDA staff will examine the application to determine whether the study is exempt. The review is limited to critical safety concerns such as dose, schedule, route, and patient population. If, after this limited review, the FDA concludes that a study is exempt from the requirement for an IND, it does not conduct any further review of the application. The FDA notifies the sponsor of the exemption by sending a letter. Before submitting the application, the sponsor can also arrange a pre-IND meeting with the FDA to discuss any questions or concerns.

When a change is made to a Phase 1 protocol that significantly affects participant safety, or to a Phase 2 or 3 protocol that significantly affects participant safety, investigation scope, or scientific quality, the sponsor of an IND must submit a protocol amendment to the FDA. Examples of changes that require a protocol amendment include increasing the drug dosage or duration of exposure, significant alterations to the study design (such as adding or removing a control group), and introducing new tests or procedures to improve safety monitoring. Once the amended protocol has been approved by the reviewing IRB and submitted to the FDA, it can be implemented at study sites.

If a protocol change is necessary to eliminate an immediate hazard to participants, it can be implemented right away. However, the FDA and reviewing IRB must be notified of the change through a protocol amendment and in accordance with the IRB's rules.

It is the responsibility of sponsors to quickly review and investigate all safety-related information they receive regarding an investigational new drug, whether it comes from domestic or foreign sources. Such information may originate from various sources, including clinical or epidemiological studies, animal studies, commercial marketing experience, reports in the scientific literature, unpublished scientific papers, and foreign regulatory authorities.

The sponsor of an investigational new drug is required to promptly investigate and review any safety-related information received from any source, be it clinical studies, animal studies, scientific literature, or foreign regulatory authorities. If there is an unexpected fatal or life-threatening experience associated with the use of the drug, the sponsor must notify the FDA as soon as possible, but within 7 calendar days of the sponsor's initial receipt of the information.

Within 15 calendar days of any serious and unexpected adverse event that is reasonably likely to have been caused by the investigational new drug, the sponsor must provide written notification to both the FDA and all investigators participating in the trial. The sponsor must also give written notification as soon as possible but no later than 15 calendar days after receiving any findings from tests in laboratory animals that suggest a significant risk for human participants. Subsequent follow-up information must also be provided as it becomes available.

To report important information about an investigational new drug (IND) that is not covered by a protocol amendment, IND safety report, or annual report, the sponsor must file an information amendment. Examples of information that require an information amendment include new information on the drug's technical features, such as its chemistry or toxicology, and the discontinuation of a clinical investigation.

Every year, within 60 days of the first anniversary of the IND's effective date and every subsequent year, the sponsor must submit an annual report on the investigation's progress. The annual report should contain a summary of the status of each study in progress or completed, a summary of the most frequent and serious adverse experiences, a summary of all submitted IND safety reports, a list of participants who died during the investigation with the cause of death for each, a list of participants who dropped out due to any adverse experience, whether or not related to the IND, a summary of the general investigational plan for the next year, an updated Investigator's Brochure (if available), a summary of any foreign market developments, and a summary of any outstanding business with the FDA regarding the IND, such as a response to an FDA request for information.

Investigational New Drugs Responsibilities

Both sponsors and investigators involved in conducting a clinical trial under an IND filed with the FDA must accept and fulfill certain responsibilities. The sponsors' responsibilities include:

- Selecting qualified investigators.
- Providing investigators with the necessary information to conduct the investigation.
- Ensuring proper monitoring of the trial.
- Ensuring the trial is conducted according to the plan and protocols contained in the IND.
- Informing the FDA and all investigators of significant new adverse effects or risks that are reasonably likely to be caused by the investigational new drug.
- Maintaining accurate records.
- Properly disposing of any unused supplies of the investigational new drug.

However, unless the sponsor is also the investigator, the sponsor is not responsible for conducting the investigation.

According to the ICH GCP E6 guidelines, sponsors have additional responsibilities, including:

- Ensuring that the investigational product is manufactured in compliance with Good Manufacturing Practices.
- Ensuring that the investigational product is packaged in a manner that prevents contamination and unacceptable deterioration during transport and storage.
- Supplying investigators or institutions with the investigational product.
- Establishing written procedures with instructions for handling and storing the investigational product that sites should follow.
- Maintaining adequate quantities of the investigational product used in the trial to confirm specifications if necessary.

These responsibilities can be delegated to a **Contract Research Organization (CRO)**, such as a clinical coordinating center, but the sponsor retains ultimate responsibility for the investigational product. Any tasks related to the investigational product that are transferred to a CRO are outlined in writing.

The following are the responsibilities of investigators:

- Submission of a completed and signed Statement of Investigator (Form FDA 1572) to the sponsor.
- Conducting the trial in compliance with the protocol, investigator statement, and relevant regulations.
- Ensuring the protection of the safety, welfare, and rights of participants in the trial.
- Acquiring informed consent from all participants in the trial.
- Keeping accurate records.
- Providing all necessary progress reports, safety reports, financial disclosure reports, and a final report.
- Following the review of the Institutional Review Board.
- Ensuring proper handling of controlled substances.

Other Investigator responsibilities based on GCP guidelines (ICH GCP E6, 4.6) include:

- Ensuring the proper labeling, storage, handling, dispensing, and disposition of the Investigational Product.
- Keeping track of Investigational Product inventory and promptly informing the sponsor if there is any significant deviation.
- Ensuring that all study-related laboratory specimens are collected, handled, and shipped properly.
- Reporting adverse events to the sponsor, IRB, and regulatory authorities as required.

- Ensuring that all study procedures are conducted in accordance with the protocol and applicable regulations.
- Maintaining adequate and accurate source documents.
- Allowing study monitoring, audits, and regulatory inspections.
- Complying with the terms of the signed investigator agreement, including financial disclosure requirements.
- Reporting any changes to the protocol or informed consent form to the IRB and sponsor, and obtaining approval before implementing the changes.

Guidance Documents:

The FDA has developed guidance documents that incorporate the principles of Good Clinical Practice (GCP) to assist researchers in complying with GCP regulations. The following documents provide guidance on Good Clinical Practice:

While not legally binding, these guidance documents represent the FDA's present perspective on the interpretation of the regulations. The FDA website provides access to numerous guidance documents, and they are also published in the Federal Register.

Chapter Twelve Resources

Summary of Key Points:

- ICH GCP defines Investigational Product as a pharmaceutical form of an active ingredient or placebo used in a clinical trial.
- According to FDA regulations, an investigational new drug is any substance for which FDA approval is being sought.
- Even if a drug has been used for years, it may be considered "new" if changes are proposed in its use, formulation, route of administration, or packaging.
- To conduct a clinical trial involving an investigational new drug, a sponsor must submit an Investigational New Drug (IND) application to the FDA, unless the drug is exempt from IND regulations.
- Behavioral studies and some medication studies may be exempt from IND regulations, but researchers should still be familiar with these regulations.

- The principle of protecting research participants applies to all studies involving human participants, regardless of whether they are subject to IND regulations.

Glossary of Terms:

ADR: *Adverse Drug Reaction*
Definition: An unwanted or harmful reaction experienced following the administration of a drug or therapeutic intervention.

AE: *Adverse Effect*
Definition: An unwanted or harmful effect resulting from the use of a drug or therapeutic intervention.

CFR: *Code of Federal Regulations*
Definition: The CFR is a collection of federal regulations organized by subject matter into 50 titles.

CoC: *Certificate of Confidentiality*
Definition: A certificate issued by the National Institutes of Health (NIH) that provides legal protection for researchers and institutions against forced disclosure of sensitive information about research participants.

CRF: *Case Report Form*
Definition: A document used in clinical trials to record the data that is collected from each participant.

CRO: *Contract Research Organization*
Definition: A company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

CV: *Curriculum Vitae*
Definition: A document that summarizes an individual's academic and professional background and accomplishments.

DEA: *Drug Enforcement Administration*
Definition: A federal law enforcement agency responsible for enforcing the controlled substances laws and regulations in the United States.

DHHS Office of Civil Rights
Definition: An office within the U.S. Department of Health and Human Services responsible for enforcing federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, sex, or religion.

DoD: *Department of Defense*
Definition: The federal department responsible for providing the military forces needed to deter war and protect the security of the United States.

DSMB: *Data and Safety Monitoring Board*
Definition: An independent group of experts that monitors the progress of a clinical trial and ensures that the study is conducted ethically and safely.

EC: *Ethics Committee*
Definition: Committee responsible for the ethical oversight of research involving human subjects, also known as an Institutional Review Board (IRB).

FDA: *U.S. Food and Drug Administration*
Definition: The federal agency responsible for protecting the public health by regulating drugs, biologics, medical devices, food, cosmetics, and other products.

GCP: *Good Clinical Practice*
Definition: Set of international ethical and scientific quality standards for clinical trials involving human subjects.

HIPAA: *Health Insurance Portability and Accountability Act*
Definition: A federal law that establishes national standards for protecting the privacy and security of individuals' personal health information.

IB: *Investigator's Brochure*
Definition: A document that provides comprehensive information on the drug or intervention being studied in a clinical trial.

ICH: *International Conference on Harmonization*
Definition: International organization that developed the current GCP guidelines, which are accepted by regulatory authorities in the United States, Europe, Japan, and other countries.

IEC: *Independent Ethics Committee*
Definition: A committee that provides independent oversight of research involving human subjects to ensure that the study is conducted ethically and with the participants' welfare in mind.

IND: *Investigational New Drug*
Definition: A drug that is being tested in a clinical trial and has not yet been approved for marketing by the FDA.

IRB: *Institutional Review Board*
Definition: Committee responsible for the ethical oversight of research involving human subjects.

NARA: *National Archives and Records Administration*
Definition: An independent agency of the United States government that is responsible for preserving and providing access to the nation's historical records.

NIH: *National Institutes of Health*
Definition: The primary federal agency for conducting and supporting medical research in the United States.

OHRP: *Office for Human Research Protections*
Definition: A federal agency responsible for protecting the rights and welfare of human research subjects in studies conducted or supported by the Department of Health and Human Services.

ORI: *Office of Research Integrity*
Definition: A federal agency responsible for overseeing investigations of allegations of research misconduct within the U.S. Public Health Service.

PHI: *Protected Health Information*
Definition: Any information about an individual's health status, health care, or payment for health care that can be linked to a specific individual.

PI: *Principal Investigator*
Definition: The individual responsible for the conduct of a clinical trial at a research site.

QA: *Quality Assurance*
Definition: A set of activities designed to ensure that the quality of the data generated in a clinical trial is reliable and accurate.

RIO: *Research Integrity Officer*
Definition: An individual responsible for ensuring that research conducted at an institution complies with federal regulations and ethical standards.

SAE: *Serious Adverse Event*
Definition: An adverse event that results in death, hospitalization, disability, or other serious adverse events.

CFR Titles

21 CFR 11: This CFR title pertains to electronic records and electronic signatures in the context of the Food and Drug Administration (FDA). It sets forth requirements for electronic records and signatures that are intended to be equivalent to paper records and handwritten signatures.

21 CFR 50: This CFR title pertains to the protection of human subjects in clinical trials conducted by the FDA. It sets forth requirements for informed consent, IRB review, and other aspects of human subject protection.

21 CFR 50.20: This CFR section sets forth requirements for informed consent in clinical trials, including the elements of informed consent that must be provided to research subjects.

21 CFR 50.25: This CFR section sets forth requirements for waivers of informed consent in emergency research situations.

21 CFR 50.27: This CFR section sets forth requirements for documentation of informed consent and IRB review.

21 CFR 54: This CFR title pertains to the financial disclosure by clinical investigators. It sets forth requirements for disclosure of financial interests in the context of clinical trials.

21 CFR 56: This CFR title pertains to IRBs (institutional review boards) that review and oversee clinical trials. It sets forth requirements for IRB composition, operations, and review of clinical trial protocols.

21 CFR 1300: This CFR title pertains to the DEA (Drug Enforcement Administration) and sets forth regulations related to controlled substances.

21 CFR 1300-end: This section of CFR title 21 contains regulations related to controlled substances that are organized by topic.

21 CFR 210: This CFR title pertains to the manufacturing, processing, packing, and holding of drugs for human use. It sets forth requirements for good manufacturing practices (GMPs) for drugs.

21 CFR 211: This CFR title pertains to the GMPs for finished pharmaceuticals and sets forth requirements for the manufacturing, processing, packing, and holding of finished pharmaceuticals.

21 CFR 312: This CFR title pertains to the Investigational New Drug (IND) application process for drugs that are not yet approved by the FDA. It sets forth requirements for IND submissions, clinical trial protocols, and reporting of adverse events.

21 CFR 312.2(b)(1): This CFR section pertains to the content and format of the IND application. This specific subsection sets forth requirements for the investigator's brochure, which is a document that provides information about the drug being studied in the clinical trial.

21 CFR 312.30: This CFR section sets forth requirements for the content and format of clinical trial protocols for drugs that are the subject of an IND application.

21 CFR 312.32: This CFR section pertains to responsibilities of sponsors and investigators for monitoring clinical trials. It sets forth requirements for reporting of adverse events and other aspects of clinical trial monitoring.

21 CFR 312.32(a): This specific subsection of 21 CFR 312.32 sets forth requirements for the reporting of serious and unexpected adverse events in clinical trials.

21 CFR 312.59: This CFR section sets forth requirements for expedited reporting of adverse events in clinical trials for drugs that are not yet approved by the FDA.

21 CFR 312.62: This CFR section pertains to the submission of annual reports by sponsors of clinical trials.

21 CFR 314: This CFR title pertains to the approval of new drugs by the FDA. It sets forth requirements for the NDA (New Drug Application) process and other aspects of drug approval.

42 CFR 2: This CFR title contains regulations regarding the confidentiality of substance use disorder patient records.

42 CFR 2.2(e): This section defines the terms "disclose," "disclosure," and "disclosed" as they relate to substance use disorder patient records.

42 CFR 2.12(c)(3): This section outlines the circumstances under which a disclosure of substance use disorder patient records is permitted for the purpose of conducting scientific research.

42 CFR 2.12(c)(5): This section outlines the circumstances under which a disclosure of substance use disorder patient records is permitted for the purpose of conducting audits or evaluations.

42 CFR 2.12(c)(6): This section outlines the circumstances under which a disclosure of substance use disorder patient records is permitted for the purpose of conducting program monitoring.

42 CFR 2.19(b)(1): This section outlines the circumstances under which a disclosure of substance use disorder patient records is permitted for the purpose of conducting a criminal investigation or prosecution.

42 CFR 2.51: This section outlines the procedures that must be followed in order to make a disclosure of substance use disorder patient records with written consent.

42 CFR 2.51(a): This section outlines the required elements of a written consent for the disclosure of substance use disorder patient records.

42 CFR 2.52: This section outlines the procedures that must be followed in order to make a disclosure of substance use disorder patient records without written consent.

42 CFR 2a: This CFR title contains regulations regarding the confidentiality of alcohol and drug abuse patient records.

45 CFR: This CFR title contains regulations regarding public welfare programs and services.

45 CFR 46: This section outlines the requirements for the protection of human subjects in research.

45 CFR 46 Subpart B: This subpart outlines the additional protections that must be provided to pregnant women, human fetuses, and neonates involved in research.

45 CFR 46 Subpart D: This subpart outlines the additional protections that must be provided to children involved in research.

45 CFR 46.114: This section outlines the requirements for obtaining informed consent from subjects who are incapable of giving informed consent.

45 CFR 46.116: This section outlines the requirements for obtaining informed consent from subjects who are capable of giving informed consent.

45 CFR 46.117: This section outlines the additional requirements for obtaining informed consent from prisoners involved in research.

45 CFR 46.303: This section outlines the requirements for obtaining documentation of informed consent in research.

45 CFR 160: This section outlines the requirements for the privacy of individually identifiable health information under the Health Insurance Portability and Accountability Act (HIPAA).

45 CFR 164: This section outlines the requirements for the security and privacy of individually identifiable health information under HIPAA.

45 CFR 164.512(j)(4): This section outlines the circumstances under which a disclosure of individually identifiable health information may be made for the purpose of conducting research.

ICH Titles

ICH E6: This refers to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline titled "Good Clinical Practice: Consolidated Guideline". It provides internationally recognized standards for designing, conducting, recording, and reporting clinical trials that involve human subjects. The guideline is intended to ensure that the rights, safety, and well-being of trial subjects are protected, and that the data generated are credible and reliable.

ICH E6(R2), 4.3: This refers to a specific section (4.3) of the updated version (R2) of the ICH E6 guideline. This section deals with the investigator's responsibilities and provides guidance on ensuring that the investigator is qualified to conduct the trial, obtains informed consent from subjects, and adheres to the protocol and applicable regulatory requirements.

ICH GCP Section 8: This refers to Section 8 of the ICH GCP guideline, which deals with the management of clinical trials. It provides guidance on the roles and responsibilities of sponsors, investigators, and monitors, as well as on the establishment of quality assurance and quality control procedures to ensure that the trial is conducted in compliance with the protocol and regulatory requirements.

ICH GCP 4.1: This refers to Section 4.1 of the ICH GCP guideline, which deals with the ethical principles that should guide the conduct of clinical trials. It emphasizes the need to respect the rights and welfare of trial subjects, to obtain informed consent, and to balance the risks and benefits of the trial.

ICH GCP 4.7: This refers to Section 4.7 of the ICH GCP guideline, which deals with the investigational product (IP). It provides guidance on the handling, storage, and

accountability of the IP, as well as on the procedures for labeling, packaging, and distribution.

ICH GCP 4.8: This refers to Section 4.8 of the ICH GCP guideline, which deals with the protocol and amendments. It provides guidance on the development and content of the protocol, as well as on the procedures for amending it.

ICH GCP 4.8.10: This refers to Section 4.8.10 of the ICH GCP guideline, which deals with the essential documents for the conduct of a clinical trial. It provides guidance on the documents that should be generated and maintained during the trial, such as the protocol, informed consent form, investigator's brochure, and case report forms.

ICH GCP 4.8.10(o): This refers to a specific subsection (o) of Section 4.8.10 of the ICH GCP guideline. This subsection deals with the maintenance of trial master files (TMF) and provides guidance on the content and organization of the TMF.

ICH GCP 4.9: This refers to Section 4.9 of the ICH GCP guideline, which deals with the monitoring of the trial. It provides guidance on the responsibilities and qualifications of monitors, as well as on the procedures for monitoring the conduct and progress of the trial.

ICH GCP 4.12: This refers to Section 4.12 of the ICH GCP guideline, which deals with the investigational site. It provides guidance on the qualifications and responsibilities of the investigator, as well as on the procedures for selecting, initiating, and supervising the site.

ICH GCP 4.13: Refers to the requirements for the investigator to maintain and retain essential documents related to the trial, including the protocol, informed consent documents, case report forms, and monitoring reports.

ICH GCP 5.1: Refers to the requirements for the sponsor to establish and maintain a quality management system to ensure that the trial is conducted in compliance with GCP and that the data generated are reliable. This includes the establishment of written standard operating procedures (SOPs) and the appointment of a qualified person to oversee the quality management system.

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