Contents

Part 1: Introduction

Documents to Ensure Standardization

Standardization — everyone doing the same things in the same way — is critical in a clinical research study and particularly critical for multisite trials. Research that is not conducted in a standardized manner is unethical because it may put research participants at risk while yielding invalid data. (Protection of the safety, rights, and well-being of research participants is discussed in the Introduction, Institutional Review Boards, and Informed Consent module.)

Several documents are key to ensuring that a research study is conducted in a standardized manner (see the module on Documentation & Record-Keeping for a full list of essential study documents). All research staff that participates in a clinical study must be familiar with, and must strictly adhere to, the procedures described in these documents.

Investigator's Brochure

The Investigator's Brochure is a document containing nonclinical and clinical data to describe previous experience with the experimental intervention, often a medication.

Operations Manual

The operations manual "operationalizes" the protocol, providing more detail on the actual procedures needed to perform the research.

For example, the protocol might specify that a urine sample is to be collected at each study visit, whereas the operations manual would describe details of the collection, labeling, storage, and shipping of the samples. For another example, the operations manual might state that each study site is to maintain a site contact log containing the names, addresses, and phone numbers of all individuals involved in the study at that site. Additionally, even more detailed information, such as a list of staff responsible for maintaining the contact log and the detailed procedures involved, would be appropriate for an Operations Manual; however, such detail would be inappropriate in the research protocol.

Standard Operating Procedures

Standard operating procedures (SOPs) describe in detail how specific procedures (e.g., taking vital signs, performing urine tests, and assessing adverse events) are to be carried out in the research study. Most SOPs will be identical for all study sites. However, in some cases site-specific variations are needed. For example, if procedures for handling a medical emergency vary slightly from one research site to another, the SOP for these procedures at a specific site will reflect those variations. Additionally, site staff will need to be trained appropriately for the site-specific procedures.

Other Study Documents

This module focuses on the research protocol. Some information may be provided in other documents that accompany the protocol, such as the Investigator's Brochure. Additional site-specific information that may change during the trial (such as the names and addresses of research sites and the sponsor's medical expert information) may be provided in a separate document, such as the operations manual. This is acceptable as long as the protocol contains language that refers to the operations manual for this information.

Research Protocol

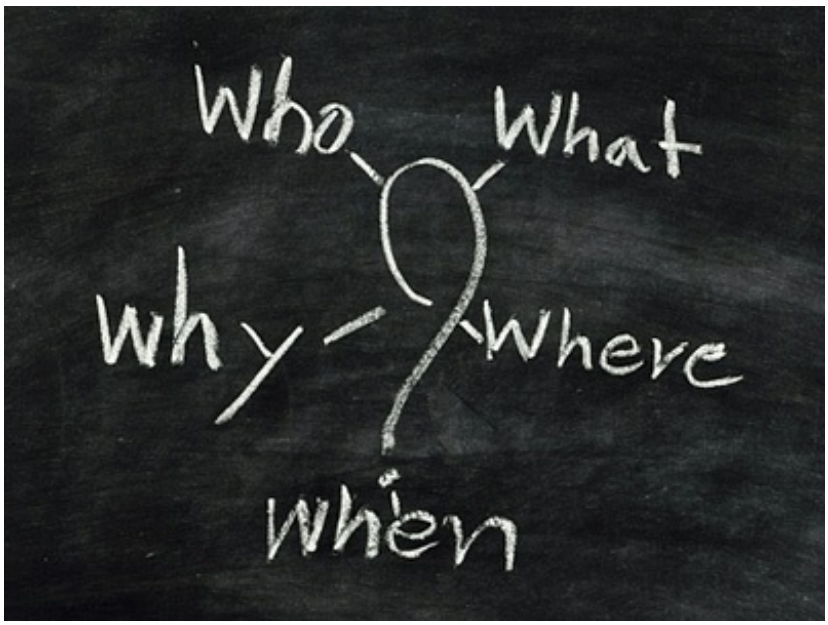
The research protocol provides a plan for the essential aspects of the proposed research. (See summarized research protocol contents.) It must be approved by the designated Institutional Review Board (IRB) before the research can begin. Any changes to the protocol must also be approved by the IRB.

Why is the research protocol so important?

The research protocol is one of the main documents that must be approved by the designated Institutional Review Board before any research study can begin.

The Good Clinical Practice (GCP) guidelines of the International Council for Harmonization require a research protocol for any study that involves human participants. In addition, Title 21 Part 312 of the Code of Federal Regulations (21 CFR 312) describes both a research protocol and protocol amendments for studies conducted under an Investigational New Drug application.

Part 2: Contents of the Research Protocol (ICH E3 GCP 6)



The research protocol must clearly and succinctly describe the following aspects of the research study:

- **Why** the study is being done.
- **What** will be done in the study.
- **Where** the study will be done (for multi-site trials, site-specific information may be incorporated into local protocal versions).
- **Who** is involved in the research study.
- **When** study interventions will take place.

The protocol should contain enough information to provide a clear and complete, but not overly detailed, description of the study. Further details should appear, as discussed earlier, in other documents such as the operations manual, standard operating procedures, quality assurance plan, training plan, and data management plan.

To ensure that research protocols include the appropriate sections and content, a sponsor may develop a standardized template for investigators to use for each type of study. For example, a research network has developed such templates to assist investigators in preparing research protocol documents for network specific trials. For NIH-funded studies under an Investigational New Drug (IND), there is a protocol template available at the following NIH website.

The protocol generally covers the following topics (see ICH GCP E6 6).

General Information

- Protocol title, identifying number, version number, and date.
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person authorized to sign the protocol and the protocol amendments for the sponsor.
- Names and titles of the investigators responsible for conducting the study, and the address and telephone number of the trial sites.
- Name, title, address, and telephone number of the sponsor's medical expert.
- Name, title, address, and telephone number of the qualified physician who is responsible for all study–related medical decisions.
- Names and addresses of all institutions involved in the study (including clinical laboratories and

other medical or technical departments).
- Addresses and telephone numbers of all clinical laboratories and/or institutions involved in the trial.

Background Information

- A description of the issue the study is addressing as well as its public health significance.
- Findings from clinical or nonclinical studies that may be significant to the proposed study.
- Summary of the known potential risks and benefits to human participants.
- A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- Description of the study population.
- References to relevant literature and data (this will often be compiled in a separate section in the protocol).
- If the study involves the use of an investigational product or therapy:
    - Name and description of the investigational product or therapy.
    - Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

Study Objectives and Purposes

A detailed description of the major (primary) and minor (secondary and exploratory) objectives and the purpose of the trial.

Study Design

The scientific integrity of the study and the credibility of the data obtained from the study largely depend on the study design. This section of the protocol should describe:

- Primary and secondary endpoints to be measured and how they will be measured.
- Study type (e.g., double-blind), with a schematic diagram of the study design, procedures, and stages.
- Measures that will be taken to avoid or minimize bias (e.g. randomization, blinding).
- Dosage and dosage regimen, dosage form, packaging, and labeling of investigational products.
- Expected duration of participant participation, sequence and duration of all study periods, including follow–up.
- "Stopping rules" or "discontinuation criteria" for individual participants, parts of the study, and the entire study.
- Accountability procedures for the investigational product, including the placebo and comparator.
- Maintenance of study treatment randomization codes and procedures for breaking codes.
- Identification of any data to be recorded directly on the CRFs and considered to be source data.

Selection and Withdrawal of Participants

- Criteria for inclusion and exclusion of participants.
- Procedures for withdrawal of participants (participant or investigator-initiated):
    - When and how to withdraw participants from the study/investigational product treatment.
    - Type and timing of data to be collected for participants who withdraw from the study.
    - Whether and how participants are to be replaced.
    - Follow–up for participants withdrawn from trial treatment.

Treatment of Participants

- Pharmacological treatment:
  - Names of all products to be administered.
  - Doses.
  - Dosing schedules.
  - Method(s) of administration (i.e., oral, intramuscular).
  - Other medications or treatments permitted (including rescue medication) and not permitted before and/or during the study.
- Other interventions (i.e., chiropractic, physical therapy, social therapy, behavioral therapy, counseling):
  - Name of intervention (i.e., Motivational Interviewing, Cognitive Behavioral Therapy).
  - Frequency of sessions.
  - Duration of each session.
  - Method of each intervention (i.e. individual, group).
  - Treatment adherence.
- All interventions:
  - Period(s) of intervention, including follow–up periods for participants in each group.
  - Procedures for monitoring participant compliance.
  - Identification of who will administer an intervention.

Assessment of Efficacy

This section describes the methods that will be used to determine the success of the treatment, including:

- Criteria for determining the treatment's effectiveness.
- Methods and timing for assessing, recording, and analyzing the effectiveness criteria.

Assessment of Safety

This section describes how the study will be monitored and how adverse events will be dealt with. (See Participant Safety and Adverse Events module.)

- Specification of safety criteria.
- Methods and timing for assessing, recording, and analyzing the safety criteria.
- Procedures for obtaining reports of adverse events and illnesses experienced by participants during the study period and for recording and reporting these events, including expedited reporting procedures.
- Type and duration of follow–up of participants who experience adverse events.

Statistics

This section describes the strategy for analyzing the data collected during the study, including:

- Statistical methods to be employed, 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.)
- Reason for the choice of sample size, including reflections on (or calculations of) the power of the study and clinical justification.
- Level of significance to be used.
- Criteria for termination of the study.
- Procedure for accounting for missing, unused, and false data.
- Procedures for reporting deviations from the statistical plan (any deviations from the statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- Selection of participants to be included in analyses (e.g. all randomized participants, all dosed or

treated participants, all eligible participants, all evaluable participants, per a stated definition of "evaluable").

Direct Access to Source Data or Documents

The sponsor should ensure that the protocol or other written agreement specifies that study investigators or institutions will permit study–related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data or documents.

Quality Control and Quality Assurance

A detailed quality assurance plan describing the set standards and controls that are in place to confirm that the execution of each step follows the agreed–upon plan is usually submitted as a separate document. The protocol should, however, provide a general description of the quality assurance methods. (See Quality Assurance module.)

Ethics

This section should describe ethical considerations relating to the study and measures taken to protect human participants and maintain confidentiality of study data. (See Informed Consent, Institutional Review Boards, and Confidentiality modules.)

Data Management

A detailed data management plan describing the way study data will be gathered, documented, submitted, verified, and archived is usually submitted as a separate document. The protocol should, however, provide a general description of the data management activities associated with the protocol.

The data management plan describes the procedures that will ensure data integrity throughout the study and at all study sites, including:

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

Financing and Insurance

This section describes how the study will be financed and insured. In some research networks, these issues are addressed in a separate agreement and need not be included in the protocol.

Publication Policy

This section describes the policies and procedures relating to publication of findings from the study. In some research networks, policies and guidelines are established for researchers for the publications planning process. For example, it is a common requirement for the publication on primary outcome data to precede other publications on the study findings. Researchers should be familiar with and adhere to institutional and sponsor policies and requirements for publications.

In accordance with the Food and Drug Administration Amendments Act (42 CFR Part 11), trial results will also be published on a public website, ClinicalTrials.gov. This website will not identify participants, but will provide a resource for clinical trial participants, and those seeking clinical trial involvement, to inform

themselves.

Supplements

This section supplies any additional information that may be required, depending on the nature of the research. For example, the informed consent template, the therapy manual, a patient information handbook, etc., may be included as attachments.

Part 2: What is a protocol violation?

Interactive: Developing the Research Protocol

Users are instructed as follows:

Of the 10 items listed below, which sections are relevant to the development of the research protocol document for a trial investigating the effectiveness of motivational counselling sessions in reducing Body Mass Index (BMI) in individuals with a BMI of 30 or more? After choosing your response, consider the feedback.

SECTION: Assessment of Efficacy

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Assessment of Safety

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Background

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Drug Accountability

Feedback: Is this section necessary for this research protocol: Yes or No? Investigational product (drug or device) is not used in this study. Therefore, Investigational Product and Drug Accountability sections should not be included in the research protocol document. The correct response is No.

SECTION: Investigational Product and Dosage

Feedback: Is this section necessary for this research protocol: Yes or No? Investigational product (drug or device) is not used in this study. Therefore, Investigational Product and Dosage and Drug Accountability sections should not be included in the research protocol document. The correct response is No.

SECTION: Quality Assurance and Monitoring

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Statistical Analysis

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Study Intervention

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Study Objectives and Design

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

SECTION: Study Population and Eligibility Criteria

Feedback: Is this section necessary for this research protocol: Yes or No? The correct response is Yes.

Part 3: What is a protocol amendment?

A protocol amendment is a written description of a change to some aspect(s) of the study as described in the research protocol.

Protocol amendments must be submitted in writing to the designated Institutional Review Board (IRB) and must be approved by the IRB before they can be implemented, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)). If the study involves a product that is regulated by the U.S. Food and Drug Administration (FDA), the amendment must be submitted to FDA as well as to the IRB, prior to enacting the amendment (21 CFR 312.30).

Protocol Amendments and Informed Consent

Study participants must be informed of protocol amendments. Depending on the nature and extent of the amendment, the Informed Consent Form may be revised, and participants will need to complete and sign a new Informed Consent Form.

A protocol amendment is not to be confused with a "protocol clarification." A protocol clarification aids in the implementation or conduct of the study and provides internal guidance. It does not change the protocol or alter the risk-benefit ratio of the study. A protocol clarification generally does not need to be submitted to the IRB. A clarification should be provided in writing to all investigators.

Part 4: What is a protocol violation?

A protocol violation occurs whenever a study staff person performs any action that does not adhere to the research protocol. Protocol violations are sometimes referred to as protocol "deviations." Although "deviations" may sound less serious than “violation,” the two terms are identical.

Protocol Violations Policy

A protocol violation may be the result of a problem with study oversight, training of study personnel, or site study procedures.

A protocol violation may be:

- An omission (i.e., failure to do something required in the protocol)
- An addition (i.e., any action that is not required in the protocol).
- A change in any procedure described in the protocol.

Protocol violations may occur due to human error. However, every attempt should be made to keep them at a minimum. Each violation and the action taken to correct the situation that led to the violation must be documented and submitted to the IRB.

Repeated protocol violations may indicate the need for additional training of research staff or the need for a protocol amendment (e.g. to allow more flexibility in a follow-up plan that participants are having a difficult time adhering to).

What to Do When a Protocol Violation Occurs

When a protocol violation occurs:

- Any concerns regarding participant safety must be addressed immediately by staff at the study site.
- The violation and a plan for corrective action must be documented.
- The violation must be reported to the principal investigator at the site, the study investigator, project management (if applicable), and the sponsor, and the FDA if the study is under an IND, in accordance with established procedures.
- The local IRB must be notified in a manner that conforms to the IRB's documented procedures.

(For a more detailed discussion of the roles of the principal investigator and lead investigator, see the Roles and Responsibilities module.)

Part 4: What is a protocol violation?

Interactive: IS THIS A PROTOCOL VIOLATION OR NOT?

Users are instructed as follows:

Consider each of the five scenarios described below. Then, classify the occurrence as a protocol violation by choosing ***Violation*** or not by choosing ***No Violation***.

Scenario 1

The clinic is approaching the end of the day. The Research Coordinator has a patient there that is eligible for the study, and he wants to quickly get through screening procedures. He decides to streamline procedures and collect the screening urine specimen before the patient has an opportunity to discuss, review, and sign the Informed Consent.

Feedback: Is this a Violation or No Violation? This is a Violation. The informed consent process communicates all of the information that the individual needs to make an informed decision about taking part in the study, before any study procedures are performed.

Scenario 2

The study protocol indicates that cash incentives are awarded based on a payment schedule, which will occur over the 12 months of the study. At each of the six study visits, the participant will receive 15 dollars in cash at the end of the visit. If the participant missed a visit or withdrew participation before the end of the study, they would not receive the reward for the missed visit(s).

The study staff at the ABC Research Clinic enrolled two participants at their site in the first week of study launch. At the first study visit, the PI determined that each participant and all future participants enrolled would receive the entire incentive ($90) at the last visit at the end of the study if the participants completed all six study visits. When the protocol monitor arrived weeks later for an interim monitoring visit, the site staff described these site procedures for applying incentives for the enrolled participants.

Feedback: Is this a Violation or No Violation? This is a Violation. Site staff did not follow the incentive payment schedule outlined in the protocol. Also, incentive payments should not be conditional on the participant's completion of the study.

Scenario 3

The protocol indicates that at the third and sixth study visits, the participant will have urine collected for drug testing. If the urine was not collected on the scheduled visit, study staff should collect at the following study visit.

At the Mercy Hospital, the clinician forgot to collect the urine specimen for drug testing on Visit 3. She collected the urine and performed the drug testing at Visit 4.

Feedback: Is this a Violation or No Violation? This is No Violation. The site staff completed the urine drug testing according to the procedures outlined in the protocol.

Scenario 4

A participant receives the wrong dose of the study medication.

Feedback: Is this a Violation or No Violation? This is a Violation. Research that is not conducted in a standardized manner is unethical because it may put research participants at risk unnecessarily while yielding invalid data.

Scenario 5

Participants are enrolled in the study although they do not meet the inclusion or exclusion criteria.

Feedback: Is this a Violation or No Violation? This is a Violation. Enrolling participants into a study that they are not eligible to participate in may put research participants at risk unnecessarily while yielding invalid data.

How to Avoid Protocol Violations

Care should be taken when writing a protocol to avoid unnecessary rigidity in schedules and procedures and to allow for flexibility whenever it does not compromise the integrity of the study or the safety of participants. This is the first step in avoiding protocol violations.

Then, every member of the research team must be familiar with the protocol and aware of the importance of following it at all times. The following steps can help to ensure that protocol violations are minimized.

- Provision of thorough protocol training as well as periodic refresher training for all members of the study team.
- Notification to all members of the study team of a protocol amendment.
- Updating research materials when changes occur such as the Informed Consent Form or Operations Manual reflecting the changes to the protocol or procedures.
- Reminders about protocol requirements during regular study team meetings.

Again, protocol violations will occur in spite of the best intentions of research staff. Violations must be documented and corrective actions taken to prevent re-occurrences.

Summary of Key Points

- Standardization of procedures is critical in a clinical research study. Research that is not conducted in a standardized manner is unethical because it may put research participants at risk while yielding invalid data.
- All research staff involved in a clinical study must be familiar with, and must strictly adhere to, the procedures described in the research protocol.
- The research protocol is one of the main documents that must be approved by a designated Institutional Review Board before a research study can begin. The research protocol provides a plan for the essential aspects of the proposed research.
- The Good Clinical Practice guidelines of the International Council for Harmonization require a research protocol for any study that involves human participants. In addition, Title 21 Part 312 of the Code of Federal Regulations requires a research protocol for studies conducted under an Investigational New Drug application.
- A protocol amendment is a change to some aspect of the study. Amendments must be approved by the IRB before they can be implemented, unless there is an immediate safety concern for participants. If the study is to be submitted to the FDA, such as being under an IND, the amendment must be submitted to the FDA as well as to the IRB.
- A protocol violation occurs whenever any study staff member performs any action that does not adhere to the study description in the research protocol. Each violation must be documented and action must be taken to correct the situation that led to the violation. Repeated protocol violations may indicate the need for additional staff training or a protocol amendment.