Research Protocol

The research protocol provides a plan for the essential aspects of the proposed research. 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 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.

Contents of the Research Protocol

General Information

- Protocol title, registration number, version number, and date.
- Names and titles of the investigators responsible for conducting the study with the address and telephone number.
- Names and addresses of all institutions involved in the study (including clinical laboratories and other medical or technical departments).
- Departments involved.
- Signed document of acceptance of general conditions and declaration.
- Recent updated curriculum vitae of the investigators

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.
- Description of the study population.
- References to relevant literature and data (this will often be compiled in a separate section in the protocol).

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**).
- 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.
- 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.

Blinding/Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). **Single blinding** usually refers to the subject(s) being unaware, and **double blinding** usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Case Report Forms

GCP defines a CRF as “A printed, optical, or electronic document designed to record all of the protocol–required information to be reported to the sponsor on each trial subject.”

Thus, a CRF may be a printed document that a study team member fills out in the clinic or an electronic document that is sent directly from a laboratory to the data management center. The purpose of CRFs is to gather study data in a standardized format so that the data can be entered into a computerized database and analyzed. The CRFs record all of the information needed to complete the data analyses used to assess the outcomes of the study. A CRF is a source document only when study data are entered directly onto the CRF, rather than extracted from another source document (e.g., progress notes).

Selection and withdrawal of participants

Recruitment to a study has two major elements:

- Defining a population of appropriate participants to answer the research question.
- Recruiting appropriate participants in an ethical manner.

The inclusion and exclusion criteria define precisely who is eligible to participate in the study and who is not. These criteria must be defined in the study protocol. They must also be carefully reviewed for every potential participant.

Inclusion criteria are the characteristics that make a potential participant eligible to enroll in a study. Generally, every potential participant must meet all inclusion criteria in order to be eligible.

Exclusion criteria are the characteristics that prohibit a potential participant from enrolling in a study. Generally, a potential participant will be ineligible if he or she meets one of the exclusion criteria.

Inclusion and exclusion criteria must be reasonable and appropriate to the study purpose. No individual or group should be excluded from eligibility to take part in the study without a valid reason. On the other hand, no individual or group should be included unless they are likely to benefit from applications of the research.

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.

- 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.
- 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 principal investigator 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.

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.

Ethics

This section should describe ethical considerations relating to the study and measures taken to protect human participants and maintain confidentiality of study data.

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.

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.

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 SGNHC research unit and Institutional Review Board (IRB) and must be approved by both 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)).

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.

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 SGNHC research unit and 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, SGNHC research unit and IRB.