Rev. 5/30/07

# Guide to Completing the Clinical Research Protocol Initial Review Application

**Principal Investigator:** There is only one principal investigator for each protocol. The PI must be an NIH employee; consultants and students may not act as principal investigators.

**Protocol Title:** Study name unique in nature and sufficiently different from other titles for easy identification. NLM restricts the title to 250 characters.

**Abbreviated Title:** Shortened protocol title consisting of 30 characters/spaces or less.

**Proposed Start**: Anticipated date enrollment is to begin.
**End Dates**: Expected date enrollment to the protocol is to close.
**Total Subjects Accrued (target table)**: maximum number of participants to be enrolled in the study. When NIH is the coordinating site report the total for the study. When NIH is not the coordinating site, report the number to be enrolled at the NIH CC. **Note:** A separate Target table must be submitted for Phase 3 and 4 Clinical Trial protocols.

**MULTI-SITE COLLABORATION:**

**Is this a multi-site collaboration?** "YES" if subjects will be accrued at more than one site. Some studies where human subjects' data/samples are analyzed outside of the NIH may also be considered multi-site studies.
**Will subjects participate on the protocol at the NIH CC?** Indicate if participants will be seen at the NIH CC.
**Will subjects participate on the protocol at other sites?** Indicate if participants will be seen at a location other then the NIH CC.
**If yes, are the sites Domestic, Foreign, or Both**. Self-explanatory
**Is NIH the Coordinating Site?**
**Yes**: For each site enrolling participants, provide the organization name, point of contact, address, and investigator(s).
**No**. Provide the name/organization of the coordinating site.

**Requested Accrual Exclusion: check all that apply:** Identify the population to be excluded from the study.

**SUBJECT ACRUAL CHARACTERISTICS**:

**Minimum/Maximum Age Permitted**: If age is not given in years, provide the unit years, months, or weeks. "N/A" should be inserted if no minimum or maximum age is intended.
**Pediatric**: select the age category of child participants to be enrolled. Select "None" if the protocol is excluding participants under the age of 18.
**Protocol involves healthy volunteers**? Indicate if the protocol will involve participants who do not have the illness under study.
**Are Healthy Volunteers NIH Employees**? Indicate if NIH Employees are eligible to participate.
**Does the protocol permit self referral**? Indicate if the study allows participants to refer themselves.
**Will the protocol involve adults unable to give informed consent**? Identify whether participants may have impaired decision-making capacity.



**PROTOCOL TYPE:**
**Screening** – Designed to determine if individuals are suitable candidates for an existing study.

**Training** – Provides the opportunity for staff physicians and other health workers to follow particular types of patients in order to maintain or increase their professional skills.

**Natural History-Disease Progression/Physiology** – Protocols designed to study normal human biology and disease pathogenesis. Such protocols may have multiple components including provisions for screening, standard therapy, physiological investigations, natural history, and long-term effects of therapy.

**Natural History-Sample/Data Collection or Analysis (Recruiting Patients)** – Protocols designed to recruit patients and collect samples/specimens or data from participants for study.

**Natural History-Sample/Data Collection or Analysis (Not Recruiting Patients)** –Protocols designed to study samples/specimens, collect data, or analyze data previously obtained. Patients will not be recruited.

**Pharmacokinetics/Dynamics** –Protocols designed to study the biochemical and physiological effects of drugs.

**Research:Clinical Trials** – Includes Phase 1 through Phase 4 clinical trials.

**Phase 0** is an initial first in human study conducted under an exploratory IND involving very limited agent exposure with no therapeutic or diagnostic intent (e.g., initial screening studies, microdose studies). The purpose of these studies is to identify the biologic and molecular markers earlier in the development of new clinical agents for improved targeted therapies before proceeding to Phase I trials. Participants in Phase 0 studies are closely monitored and conducted in patients or normal volunteers. The total number of study participants varies with the drug and the clinical condition but usually includes no more than 20 – 30.

**Phase 1** includes the introduction of an investigational new drug into humans. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase I, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase II studies. Participants in Phase I studies are closely monitored and may be conducted in patients or normal volunteer volunteers. The total number of patients and volunteers included in Phase I studies varies with the drug, but is generally in the range of 20-80.

**Phase 1-2** includes both phase 1 and phase 2 procedures into a single trial. These studies are initiated when there is an expectation of less than usual short-term side effects and risks associated with the drug or biologic such as vaccine trials. Once the metabolic and pharmacologic actions of the drug and the side effects are determined then the trial moves directly into determining the effectiveness of the agent. As with Phase I and II studies, the participants are closely monitored and as with phase II trials involve several hundred participants.

**Phase 2** includes the controlled and uncontrolled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Participants in Phase II studies are typically closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred participants.

**Phase 3** studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. Phase III studies usually include from several hundred to several thousand participants under both sponsor and FDA safety monitoring.

**Phase 4** (From CFR 312.85) Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase IV) studies to delineate additional information about the drug's risks, benefits, and optional use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

**If a Phase 3 Clinical Trial, is analysis for sex, racial/ethnic subgroups required according to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research?** NIH policy requires investigators to report annual progress in conducting analyses for gender, and racial/ethnic differences. The only exception to this requirement is when data from prior studies strongly support no significant difference in intervention effect based on gender, racial./ethnic and/or relevant subpopulation comparisons. Refer to the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

**Key Words**: Provide up to 10 words that describe the study and not contained in the study. Do not use numbers.

**Ionizing Radiation Use**: Check **ALL** applicable boxes.

**Medically Indicated**: If radiation exposure is used for clinical management of the participants.

**Research Indicated**: If participants are exposed to radiation for research purposes, without clinical utility.

**Investigational New Drug/Device**: defined as a new drug or biological agent that is used in a clinical investigation.

**FDA No**. – Number assigned by the FDA

**IND/IDE Name:** Name of the investigational drug, biological agent, or device.

**Sponsor**: The person/organization/institution/company who takes responsibility for the clinical investigation. A sponsor of a clinical trial is the IND holder and will usually supply the drug or device for the trial, monitor the clinical trial, and report to the FDA. The sponsor can be an individual, commercial entity (e.g., drug company), government agency (e.g., Cancer Therapy Evaluation Program), academic institution, or clinical trial organization (e.g., cooperative group operations office).

**Who is the manufacturer of the above entity**: Commercial entities that manufacture the investigational drug/device, supply the drug/device for the trial, hold the IND and sponsor the trial, or are a partner in the development of the drug/device should be reported.



**Does the protocol involve a Tech Transfer Agreement?** Identify if the protocol involves a technology transfer agreement with an outside organization. If it's not clear, check with your IC Technology Transfer Representative.

**Does the protocol involve a drug/device/product that may lead to you or the NIH to receive payment and/or royalties?** Refer to the Guide to Preventing Conflicts of Interest. http://intranet.cc.nih.gov/od/conflict_interest/conflict_memo.shtml

**Has the NIH IRP COI Guide been distributed to NIH Investigators?** NIH requires the guide to be distributed to NIH Investigators.

**Has the NIH IRP COI Guide been distributed to Non-NIH Investigators?** NIH requires the guide to be distributed to non-NIH Investigators.

**CONFLICTS OF INTEREST REVIEW:**

**Date submitted to IC DEC:** Date the Protocol Conflict of Interest Statement was sent to the PI's Deputy Ethics Counselor (DEC).

**Date cleared by IC DEC:** Date the Deputy Ethics Counselor signed the Protocol Conflict of Interest Statement.

**INVESTIGATOR ROLES:**

**Adjunct Principal Investigator**: an individual serving as the principal investigator who is not an NIH employee. If the protocol has an Adjunct Principal Investigator, there must be a named NIH Principal Investigator who is an employee and who will be responsible for the conduct and conflicts analysis of the protocol. The relationship between the Adjunct PI and the NIH PI will allow for the conduct of collaborative protocols between the intramural and extramural/outside medical community.

**Medical Advisory Investigator**: Assists in the development of the clinical aspects of the protocol and advises the PI on clinical matters. An MAI must be identified when the PI is not a member of the Junior or Senior Staff, or when the Clinical Director, IRB, or Director, CC, consider it warranted. The MAI must be a member of the CC Junior or Senior Medical Staff. *Medical management of the protocol. (B. Karp) J. Lambert comments..*

**Lead Associate Investigator**: an individual who played a leading role in the formulation, writing, and implementation of a clinical research protocol under the mentorship of the protocol's principal investigator. A lead associate investigator may be a physician, a dentist, a Ph.D., an RN, a member of the allied health professions, or a trainee.

**Research Contact**: the individual to whom potential participants may be referred.

**Associate Investigator(s)**: an individual, other than the principal investigator, who makes substantial contributions to the study.

**Accountable Investigator**: tenured or tenure-track investigators or senior clinicians who are responsible and accountable for the scientific quality and expenditure of resources for the protocol. The Accountable Investigator may be the Branch Chief or Department Head.

**Page 2 of the NIH 1195** (Data elements required by the NLM for posting on clintrials.gov)

**Conditions**: Primary diseases or conditions being studied. The conditions are used for search purposes by the Patient Recruitment and Public Liaison Office as well by the National Library of Medicine to index. It is preferred that the terms are selected from the controlled vocabulary MeSH. http://www.nlm.nih.gov/mesh/MBrowser.html

**STUDY TYPE**: Nature of the Investigation. Must select Interventional or Observational and under each, the most appropriate term describing the protocol for each category.

**Interventional**: experimental studies in humans to investigate the safety and/or efficacy of a drug, gene therapy, vaccine, behavior, device, or procedure.

**Purpose**: reason for the protocol

- **Treatment**: protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition.
- **Prevention**: protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition
- **Diagnosis**: protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition.
- **Educate/Train**: protocol designed to assess one or more interventions in an educational, counseling, or training environment
- **Supportive Care**: protocol designed to evaluate interventions where the primary intent is to maximize comfort, minimize side effects or mitigate against a decline in the subject's health or function. In general, supportive care interventions are not intended to cure a disease.
- **Screening:** protocol designed to assess or examine methods of identifying a condition (or risk factors for a condition) in people who are not yet known to have the condition (or risk factor).
- **Health Services Research:** protocol designed to evaluate the delivery, processes, management, organization or financing of health care.

**Study Design**: participant selection.

- **Randomized Trial**: participants are assigned to intervention groups by chance
- **Nonrandomized Trial**: participants are expressly assigned to intervention groups

**Masking**: knowledge of intervention

- **Open**: no masking is used. All involved know the identity of the intervention assignment.
- **Single Blind**: one party, either the investigator or participant, is unaware of the intervention assignment; also called single-masked study.
- **Double Blind**: both participants and investigators are unaware of the intervention assignment

**Control**: nature of the intervention control

- **Placebo**: participants may receive only placebo throughout the course of the protocol
- **Active**: participants may receive some form of treatment (e.g., standard treatment) in place of the intervention under investigation
- **Uncontrolled**: no controls are used
- **Historical**: the control consists of results from past studies
- **Dose Comparison**: participants may receive one of several doses of the intervention

**Assignment**: intervention groups

- **Single Group**: single arm study
- **Parallel**: participants are assigned to one of two or more groups in parallel for the duration of the study
- **Cross-over**: participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study
- **Factorial**: two or more interventions, each alone and in combination, are evaluated in parallel against a control group

**Endpoint**: primary outcome that the protocol is designed to evaluate.

- **Safety:** show if the drug is safe under conditions of proposed use
- **Efficacy**: measure of an intervention's influence on a disease or health condition
- **Safety/Efficacy:** includes outcomes of safety and efficacy
- **Bio-equivalence**: scientific basis for comparing generic and brand name drugs
- **Bio-availability**: rate and extent to which a drug is absorbed or otherwise available to the treatment site in the body
- **Pharmacokinetics**: the action of a drug in the body over a period of time including the process of absorption, distribution and localization in tissue, biotransformation, and excretion of the compound
- **Pharmacodynamics**: action of drugs in living systems
- **Pharmacokinetics/Pharmacodynamics:** includes outcomes of pharmacokinetics and pharmacodynamics

**Observational**: studies in humans that record specific events occurring in a defined population without any intervention by the researcher, such as natural history, screening, and some psychosocial studies.

**Purpose**: reason for the protocol

- **Natural History**: protocol designed to investigate a disease or condition through observation under natural conditions (i.e., without intervention)
- **Screening**: protocol designed to assess or examine persons or groups in a systematic way to identify specific markers or characteristics (e.g., for eligibility for further evaluation)
- **Psychosocial**: protocol designed to observe the psychosocial impact of natural events

**Duration of Sampling**: protocol sample in
- **Longitudinal**: studies in which participants are evaluated over long periods of time, typically months or years
- **Cross-sectional**: studies in which participants are evaluated over short periods of time, typically up to 10 weeks

**Selection Method**: sample selection
- **Targeted Population**: participants or populations are selected based on predefined criteria
- **Random Sample**: participants or populations are selected by chance
- **Case Control**: participants or populations are selected to match the control participants or populations in all relevant factors except for the disease; only the case participants or populations have the disease

**Timing**: data collection period
- **Retrospective**: a protocol that observes events in the past
- **Prospective**: a protocol that observes events in real time (may occur in the future)
- **Both**: a protocol that combines retrospective and prospective observation

**Interventions**: *Required for interventional studies **only**.* Primary intervention(s) studied. Provide specific category for each intervention (up to 10 items).

Drug
Gene Transfer - *including gene transfer and recombinant DNA* (e.g., Human nerve growth factor)
Vaccine
Behavior (e.g., Protein and calorie controlled diet; Self-hypnotic relaxation)
Device (e.g., Defibrillators, implantable; Electronic medication reminder system)
Procedure (e.g., Adenoidectomy; Bronchoalveolar lavage)

**Outcome Measure(s)/Endpoint(s)**: *Required for interventional studies **only**.* Specific measurements or observations used to measure the effect of experimental variables in a study.

**Primary**: the specific measure that will be used to determine the effect of the intervention(s). (limit 254 characters/spaces)
**Secondary**: Other key measures that will be used to evaluate the intervention(s), and that are specified in the protocol. (limit 254 characters/spaces)