FULL PROTOCOL TITLE

(If not obvious from the protocol title, consider adding a subtitle that briefly summarizes the trial, such as: A randomized, placebo-controlled, double-masked, 2100-subject clinical trial of X in the treatment of Z.)

Study Chair:

(List Study Chair's name, degree, position and affiliation)

Supported by:

The National Institute of Neurological Disorders and Stroke (NINDS)

(Include application or grant number(s) when available)

Study Intervention Provided by:

(Name of pharmaceutical company or device manufacturer, if any, providing support)

Sponsor of IND (IDE):

(Official sponsor, i.e., IND or IDE holder, if any. Include IND/IDE # when available)

(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

Version 1
Month Day, Year

TABLE OF CONTENTS

SYNOPSIS

The following sections should provide a bare-bones outline of approximately 1-2 pages.

Study Title

Specify the full title (and subtitle, if applicable) of the study.

Objectives

Specify the primary and secondary objectives.

Design and Outcomes

Provide a very brief description of the study design (e.g., multicenter, randomized, double-masked, Phase III), including the outcome variables for the primary and, if applicable, secondary objectives.

Use brief overview diagram here, if applicable. Complex diagrams may be included in Section 3, Study Design, instead.

Interventions and Duration

Briefly describe the interventions to be compared. Indicate the total length of time each subject will be on study (intervention period + additional followup off intervention, as applicable).

A brief statement about the schedule and type of evaluations to be performed during the study may also be included.

Sample Size and Population

Briefly describe the number and type (patient population) of subjects to be studied.

If the randomization will be stratified, list the stratification factors. If there will be separate objectives and outcome variables for the strata, list these in the appropriate sections (above).

1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective should always be to address a specific hypothesis. State the hypothesis in quantifiable terms; e.g., "the experimental treatment will result in 12 months of additional survival compared to the control treatment." For statistical purposes, it may be worthwhile to state both the null and the alternative hypotheses. This primary objective must match the one used in section 9, Statistical Design.

1.2 Secondary Objectives

Secondary objectives may or may not be hypothesis-driven, may include secondary outcomes, and may include more general non-experimental objectives (e.g., to develop a registry, to collect natural history data).

2 BACKGROUND

2.1 Rationale

Describe the patient population to be studied and justify any restrictions on the population. Name and describe the intervention regimens, and justify why these particular interventions have been chosen. Describe and justify the route of administration, dosage regimen, intervention period, etc. Spell out the need, relevance and priority for the study.

2.2 Supporting Data

Provide the scientific and medical data (e.g., results of Phase I and II studies) that justify the study, its design, and the intervention groups.

Summarize the known and potential risks of the interventions. For drug studies, package insert information can be referred to, but does not need to be included unless there is a new, significant change. Justify any aspects of the study not FDA-approved (e.g., different dosing schedule, new combination of drugs, new drug formulation).

3 STUDY DESIGN

Briefly describe the study design and indicate, in general terms, how the design will fulfill the intent of the study. Use diagrams to explain design complexities.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.1 *The disease or disorder under study, and how it is to be documented, i.e., diagnostic methods, criteria for classification, etc.*

4.1.2 *Clinical indicators of current status, as measured within XX days of randomization.*

4.1.3 *Prior therapy, if any. Consider listing specific prior treatments. Consider listing the allowable duration of prior therapy for the specific population to be studied (e.g., treatment-naïve, treatment-experienced, or prior-treatment-failed "salvage" subjects).*

4.1.4 *Demographic characteristics (e.g., gender, age) as applicable*

4.2 Exclusion Criteria

4.2.1 *List specific clinical contraindications. Specify grades of signs/symptoms.*

4.2.2 *Clinica/laboratory indicators of current status, obtained within XX days prior to randomization. List the specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion, consistent with safety.*

4.2.3 *Specify any exclusion related to pregnancy, lactation, or plans to become pregnant. Specify methods for assessing current status and willingness to use contraception, if applicable.*

4.2.4 Use of *[excluded drugs, devices, etc.]* within XX days prior to study entry.

4.2.5 *For drug studies:* Allergy/sensitivity to study drugs or their formulations.

4.2.6 *Specify any clinical (e.g., life expectancy, co-existing disease), demographic (e.g., age) or other characteristic that precludes appropriate diagnosis, treatment or follow-up in the trial.*

4.2.7 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.8 Serious illness (requiring systemic treatment and/or hospitalization) until subject either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least XX days prior to study entry. *List specific illnesses and acceptable time.*

4.2.9 Inability or unwillingness of subject or legal guardian/representative to give written informed consent.

4.3 Study Enrollment Procedures

4.3.1 *Describe in detail the methods for identifying and recruiting candidates for the trial.*

4.3.2 *Describe procedures (e.g., maintaining a screening log at each clinical site) for documenting how subjects learned about the trial, who referred them to the trial, reasons for ineligibility, and reasons for nonparticipation of eligible subjects. Describe how this information will be collected centrally and used to enhance subject recruitment efforts.*

4.3.3 *Describe consent (and assent) procedures.*

4.3.4 *Describe the procedure for obtaining intervention group assignment.*

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Indicate each study intervention, including how it is administered and the schedule, as well as potential side effects. Indicate where the subject will be treated (e.g., intensive care unit). State guidelines for use of appropriate supportive care medications or treatments.

5.2 Handling of Study Interventions

Describe how the interventions are to be acquired by the participating clinical sites (e.g., the pharmaceutical company will distribute the drug in bulk to the site pharmacist), and how they are to be stored, prepared, and dispensed. If applicable, describe the disposition of unused study products (e.g., materials to be returned to the pharmaceutical or device company supplying them). Describe procedures for documenting study intervention accountability. If appropriate, reference the study's Manual of Operations for detailed instructions on these issues.

Note mechanisms (if any) for masking (i.e., blinding) study interventions. For example, if a placebo is being used in a drug trial, note whether it has similar color, taste, etc., as the active drug.

5.3 Concomitant Interventions

Required, prohibited, and precautionary interventions (e.g., medications) will depend upon the interventions used in the study and the outcomes of the study. Interventions not listed in sections 5.3.2-5.3.3 are permitted.

5.3.1 Required Interventions

5.3.2 Prohibited Interventions

Include drugs, devices, etc. from the exclusion criteria (section 4.2.4) if they are also prohibited while the subject is on study.

5.3.3 Precautionary Interventions

Include instructions for modifications to the study interventions, if appropriate.

5.4 Adherence Assessment

Indicate whether compliance of subjects with the study intervention is to be assessed. If so, provide details as to how this will be carried out (e.g., pill counts, electronic monitoring devices, adherence questionnaires), and in the section on Data Analyses (Section 9.5), describe how this information will be incorporated into the analysis of the study results.

6 CLINICAL AND LABORATORY EVALUATIONS

The Schedule of Evaluations in section 6.1 should include all study evaluations. Use an 'X' in a cell to indicate that a particular evaluation is to be performed at a particular study visit.

The definitions for the Schedule of Evaluations included in section 6.2 define the evaluations, provide timelines, and include special considerations or instructions for evaluations.

The evaluations listed and their order in the table are only examples! The evaluations should be specific for the particular protocol and should be arranged for clearest presentation. Additional columns may be needed to specify evaluations at intervention failure, at premature discontinuation of study interventions, or at other special timepoints that require a different set of evaluations. In complicated studies with multiple study steps or multiple randomization points, it may be useful to include in the table the time of each step/randomization and the time that study intervention is given to the subject.

6.1 Schedule of Evaluations

Evaluation	Screening (-XX days)	Pre-Entry (-XX days)	Entry	4 wk	8	12	16	20	24	32	40	48
Informed Consent												
Documentation of Disease/Disorder												
Medical/Treatment History												
Clinical Assessment												
[Complete/Targeted] Physical Exam												
[Other Clin. Assess. components if on a different schedule]												
Hematology												
Chemistry												
Liver Function Tests												
Urinalysis												
Pregnancy Testing												
Stored Plasma												
Stored Serum												
Adherence Assessments												
Questionnaires												

6.2 Timing of Evaluations

This section should include definitions of the column headings in the Schedule of Evaluations and any special instructions.

6.2.1 Pre-Randomization Evaluations

These evaluations occur prior to the subject receiving any study interventions.

Screening

Specify allowable range of time prior to study entry during which all screening evaluations to determine eligibility must be completed. Indicate whether screening and pre-entry evaluations must be separated by a certain number of days or hours, or whether screening and pre-entry evaluations may occur concurrently. If screening involves performing procedures that are not part of routine patient management, indicate procedure to obtain informed consent for screening.

Pre-Entry

For subjects who have successfully been screened for eligibility and are slated to be randomized into the study, specify allowable windows for pre-entry evaluations relative to screening evaluations and study entry.

Entry

Specify time window for (a) study entry (i.e., randomization) relative to completion of pre-entry evaluations and (b) initiation of study intervention relative to study entry.

If entry evaluations are to be made after randomization, the column should be moved under On-Study Evaluations.

6.2.2 On-Study/On-Intervention Evaluations

Indicate schedule of evaluations occurring after randomization while the subject is on-study and on (or about to start) intervention. Include allowable time window in which evaluations may take place, e.g., study visits must be scheduled on the weeks indicated in the Schedule of Evaluations ± 7 days.

6.2.3 Intervention Discontinuation Evaluations

Specify evaluations needed for subjects at the time of discontinuation of study intervention. Define "intervention discontinuation" if necessary.

Also specify evaluations needed for subjects who prematurely discontinue study intervention if these differ from those for subjects who completed the full treatment course expected under the protocol. Note that for trials following an intention-to-treat design, subjects who discontinue intervention should continue to be followed and evaluated on study. Describe efforts to be made to retain such subjects on study and, when practical, to encourage them to resume study intervention.

6.2.4 On Study/Off-Intervention Evaluations

Indicate the schedule for evaluations to be completed while the subject is "off intervention/on study," i.e., no longer on study intervention but still being followed for outcomes, if applicable. Indicate evaluations needed for subjects who complete scheduled study intervention and for subjects who prematurely discontinue from study intervention, if applicable

6.2.5 Final On-Study Evaluations

Indicate the schedule for procedures to be completed at the subject's final visit on study.

6.2.6 Off-Study Requirements

Specify any requirements for followup on subjects once they have completed the protocol-specified period on study intervention. For example, it may be appropriate to ask the subject to return to the site two weeks or so after the subject goes off study in order to evaluate the subject for any adverse effects and to provide further information about options for future clinical care.

6.2.7 Pregnancy *(Optional)*

Specify instructions for women who become pregnant while on-study. If they are allowed to remain on study, specify whether they must sign a pregnancy consent form (refer to appropriate appendix) and whether additional evaluations are needed.

6.3 Special Instructions and Definitions of Evaluations

This section should explain the rows of the table of the Schedule of Evaluations from top to bottom. Specify the data items that must be included in the source document.

6.3.1 Informed Consent

Describe patient education and informed consent process; any plan for review of consent document in case changes may be required; and how documentation of signed consent will be maintained by the study.

A model informed consent form should be included as an appendix to the protocol. When developing the consent form, consider including language allowing for the retention of study data and specimens beyond the close of this study, for sharing the de-identified data and specimens with other researchers, and for using the specimens for purposes beyond the scope of this study.

6.3.2 Documentation of *[specify the Disease/Disorder under study]*

Include clinical, laboratory, radiological or other recognized methods of documenting the disease or disorder from subject's source document.

6.3.3 Medical History

6.3.4 Treatment History

6.3.5 Concomitant Treatments

6.3.6 Study Intervention Modifications

6.3.7 Clinical Assessments

Define which clinical parameters are measured and when. A physical exam, if required, should be specified as targeted or complete. Specify which clinical events should be recorded on the CRFs. NINDS strongly encourages investigators to make use of the NINDS Common Data Elements in developing the CRFs (see http://www.commondataelements.ninds.nih.gov/).

6.3.8 Laboratory Evaluations

Specify grade and recording instructions.

6.3.9 Pharmacokinetic Studies

This section is applicable for studies involving drugs as study interventions and when pharmacokinetics are being performed. Pertinent additional information can be included in an appendix.

6.3.10 Other Laboratory Studies

Other laboratory studies (e.g., metabolic studies) and special tests should also be explained.

6.3.11 Additional Evaluations

6.3.12 Questionnaires

Include subject and caretaker interviews regarding quality of life, etc.

6.3.13 Adherence Assessments

7 MANAGEMENT OF ADVERSE EXPERIENCES

Include:
- *A list of expected adverse experiences for each study intervention*
- *Criteria for subject management and modification of the study intervention regimen*
- *Procedures for modification (forms, additional labs, and change in regimen)*
- *List alphabetically by adverse experience*

For investigational drug studies, the Study Chair should work closely with the pharmaceutical company representative to ensure that toxicities that have been seen in previous studies are identified, and that a plan for management and documentation of these toxicities is developed.

8 CRITERIA FOR INTERVENTION DISCONTINUATION

List criteria for discontinuing intervention and methods for determining when criteria are met. Include procedures for maintaining subject participation in followup activities.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Describe general design issues including:
- *Primary and secondary hypotheses and how they relate to choice of primary and secondary outcome measures;*
- *The validity and reliability of the primary and secondary outcome measures;*
- *Whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be masked to the subject's intervention group assignment;*
- *Choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial);*
- *Details of why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen);*
- *What factors (if any) will be used to stratify the randomization;*
- *If each subject is to be followed for a fixed followup period (e.g., to 24 months) rather than to a common closeout date (e.g., 24 months following enrollment of the last subject), clarify why the particular fixed time period was chosen.*

Statisticians sometimes use computer simulations to investigate the operating characteristics of complex clinical trial designs (such as adaptive designs), to choose between alternative outcome measures, or to determine sample size, taking into account the impact of such factors as noncompliance, losses to followup, missing data, and subject eligibility criteria (risk profile). If simulations were performed to aid in the design of this clinical trial, sufficient details about the simulations should be provided (possibly in an appendix to the trial protocol) to assure that the simulations were performed and analyzed in a valid manner. See the article, "The design of simulation studies in medical statistics", by Burton et al., Statist. Med. 2006: **25**:4279-4292 *for guidance on how to document a simulation study. It is particularly important to discuss the range of conditions that were considered in the simulation and why was this range was considered appropriate, how robust the findings were across the range of conditions considered, and how the study will adjust for any design deficiencies (e.g., bias, loss of power) the simulations reveal.*

9.2 Outcomes

9.2.1 Primary outcome *(including definition)*

9.2.2 Secondary outcomes

9.3 Sample Size and Accrual

Describe the statistical and clinical bases for the sample size calculation. State the assumptions made regarding accrual rate, event rate, noncompliance rate, loss-to-followup rate, and Type I and II errors. Describe the plan for compensating for failures in these assumptions. Also describe what the power will be for assessing secondary outcomes.

If the randomization will be stratified, indicate whether (and why) there is a sample size goal for each stratum.

9.4 Data Monitoring

The NINDS Guidelines on Data and Safety Monitoring generally require that a NINDS-appointed Data and Safety Monitoring Board monitor Phase III clinical trials. Describe the interim monitoring plan, including the schedule of interim analyses and guidelines for stopping the study for reasons of efficacy, safety, futility, or poor study performance (e.g., slow accrual, high losses-to-followup, poor quality control). Note that interim monitoring (for safety and study performance, at least) must be done at least annually following the randomization of the first subject. If the study includes stratification factors, indicate whether there are separate monitoring considerations for each stratum.

9.5 Data Analyses

List the statistical methods to be used to analyze the primary and secondary outcomes. Specify any confounding variables for which it is anticipated adjustment will be made. Specify whether an Intention-to-Treat analysis will be performed, and explain how missing data, outliers, noncompliance and losses to followup will be handled in the analyses.

In accordance with NIH policy, if data from prior studies do not negate strongly the existence of significant differences of clinical or public health importance in the intervention effect between gender and racial/ethnic subgroups, a statement should be included noting that a valid analysis of the intervention effect will be performed in these subgroups. If data from prior studies do not support strongly the existence of significant differences in the intervention effect between subgroups, then the analyses need not have high statistical power for detecting clinically meaningful differences.

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1 Records to Be Kept

Indicate what information will be retained for each subject and by whom. Describe methods for maintaining confidentiality of subject records.

10.2 Role of Data Management

10.2.1 *Briefly describe clinical site responsibilities in data collection and management.*

10.2.2 *Briefly describe Statistical Center responsibilities in data management.*

10.3 Quality Assurance

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, ethical standards, regulatory compliance and data quality at the clinical sites, including review of records, consent forms, etc. Note that clinical sites are required to make study documents and pertinent records available for inspection by monitoring authorities.

10.4 Adverse Experience Reporting

Indicate how adverse experiences are to be recorded and reported, and within what timeframe. Mention that all FDA, OHRP and local IRB requirements for reporting adverse experiences must be followed. Detailed definitions of adverse experiences, a table for grading their severity, and details of how clinical sites are to report them, may appear in a separate Manual of Operations, which may be referred to here.

11 HUMAN SUBJECTS

The texts in this section are examples only.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix XX) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, the sponsor, or the sponsor's designee.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Sample text:

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NINDS prior to submission.

13 REFERENCES

Provide the citations for all publications and presentations referenced in the text of the protocol.