Detailed Protocol Narrative

The protocol narrative (or "protocol") is submitted with the initial submission of the study and revised versions are submitted, as necessary, with amendments. It must be sufficiently detailed to permit the IRB to evaluate the soundness of the procedures proposed and the potential risks and benefits to research subjects. For clinical trials, the latest version of the protocol must be provided for review; sponsor protocol may be provided in lieu of a local protocol.

The protocol should include page numbers and section headings. As a general guideline, the following sections are appropriate:

1. background and prior pertinent experimental findings or animal data, if any. This is required for studies of investigational drugs or investigational devices;

2. purpose or hypothesis of the study, including potential knowledge to be gained and noting specific aims;

3. description of protocol methodology;

4. special precautions to be taken by researchers, including dose modifications;

5. description of experimental controls and use of placebos;

6. if applicable, the protocol should state who will infuse the patients with drugs, how it will be done, where it will be done, and what the individual's background and training is;

7. description of anticipated coordination between appropriate inter-departmental faculty, and where necessary inclusion of those faculty as participants;

8. probable duration of protocol;

9. exact location where research is to be conducted (building, room number, etc.);

10. type and number of experimental subjects, including method of subject selection, randomization, and inclusion and exclusion criteria, if any;

11. description of how the subject's primary physician will be notified of and, as appropriate, involved in the proposed research;

12. description of recruiting methods (i.e., advertisements, patient records, primary physician referrals). If ads are to be used, indicate where ads will be placed and who will handle responses to the ads;

13. any payment to subjects;

14. procedures to obtain informed consent, including initial and subsequent consent discussion(s);

15. procedures to document consent;

16. potential risks and benefits to subjects;

17. plan for monitoring of safety of subjects, including a plan for reporting adverse events to the IRB, sponsor, and the FDA, as applicable. If a Data Safety Monitoring Board (DSMB) will be utilized, this should also be described;

18. procedures which will be used to maintain confidentiality of research and subject materials including specific description as to what methods would be used;

19. inclusion of statistical justification to justify the number of subjects to be enrolled;

20. description of the statistical analysis to which the data will be subjected, to address each specific aim and to ensure that the study will produce statistically valid conclusions to justify the research on human subjects;

21. bibliographic references to support the hypothesis and the justification for the use of human subjects and in particular the inclusion of any vulnerable populations;

22. other sections as applicable, including:

    a. if applicable, the protocol should clarify whether subjects will be asked to take a pregnancy test before and, as applicable, during the study. The IRB suggests the following guidelines for testing: presence or absence of serum HCG (pregnancy test) should be determined no earlier than the seventh day of the luteal phase (i.e., not earlier than day 21 in women with 25 day cycles, not earlier than day 22 in women with 29 day cycles, not earlier than day 23 in women with 30 day cycles, etc.);

    b. as applicable, a rationale for excluding women, minorities and/or children from participation. National Institutes of Health require that all research involving human subjects includes women, minorities and children. All protocols that explicitly exclude any of these populations must provide sufficient rationale for the exclusion of such. Sufficient rationale might include a discussion of the inappropriate study population with respect to the health of the subjects or the purpose of the research. The expectation that additional costs may be incurred by including women, minorities and children cannot be a reason for excluding these populations. Note that inclusion of children will involve additional review requirements by the IRB.

    c. In addition to other requirements, per **21CFR312.23(a)(6),** the FDA will require the following in a protocol document to support an IND application:

(i) A protocol for each planned study. … In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation - an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose - and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring

of vital signs and blood chemistries. …

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of nonresponders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.

(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.