

The Clinical Protocol

As a part of the IND application, a clinical protocol must be submitted to ensure the appropriate design and conduct of the investigation. Clinical protocols include

- Statement of the purpose and objectives of the study
- Outline of the investigational plan and study design, including the kind of control group and methods to minimize bias on the part of the subjects, investigators, and analysts
- Estimate of the number of patients to be involved
- Basis for subject selection, with inclusion and exclusion criteria
- Description of the dosing plan, including dose levels, route of administration, and duration of patient exposure
- Description of the patient observations, measurements, and tests to be used
- Clinical procedures, laboratory tests, and monitoring to be used in minimizing patient risk
- Names, addresses, and credentials of the principal investigators and coinvestigators
- Locations and descriptions of the clinical research facilities to be used
- Approval of the authorized IRB

Once an IND is in effect, a sponsor must submit an amendment for approval of any proposed changes. This may involve changes of dosing levels, testing procedures, the addition of new investigators, additional sites for the study, and so on.

For many years, women and the elderly were included only rarely in clinical drug investigations. Women of childbearing age were excluded from early drug tests out of fear that the subject would become pregnant during the investigation with possible harm to the fetus. Exceptions were made only in cases of potentially lifesaving drugs. However, in recognition that the general exclusion of women from drug investigations results in inadequate data on any gender-based differences in a drug's effects, the FDA now calls for the inclusion of women in numbers adequate to allow detection of

clinically significant differences in drug response.

The FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs issued in 1993 states the agency's gender inclusion policy (39). Although the guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analysis of clinical data by gender, and assessment of potential pharmacokinetic differences between genders. In 1994, the National Institutes of Health (NIH) similarly issued its policy that women and minorities be included in all NIH-supported biomedical and behavioral research projects involving human subjects "unless there is a clear and compelling rationale and justification that their inclusion is inappropriate with respect to the health of the subjects or the purpose of the research" (40).

Pregnancy is a concern in drug investigations because drugs are readily transported from the maternal to the fetal circulation. Because of undeveloped drug detoxication and excretion mechanisms in the fetus, concentrations of drugs may actually reach a higher level in the fetus than in the maternal circulation, with toxic levels resulting. To reduce the risk of fetal exposure to investigational drugs in women of childbearing age, the FDA guideline calls for pregnancy testing, use of contraception, and full information disclosure of potential fetal risks to prospective study subjects. The FDA has made a special effort to ensure that women who have a life-threatening disease (e.g., AIDS-related) are not automatically excluded from investigational trials of drug products for that disease because of a perceived risk of reproductive or developmental toxicity from use of the investigational drug. There are other instances in which drug studies or drug use during pregnancy is justified, for example, agents intended to prevent Rh immunization and hemolytic disease of the newborn (41).

When a proposed drug is likely to have significant use in the elderly, elderly patients are required to be included in clinical studies to