GUIDELINES FOR THE CLINICAL EVALUATION OF LIPID-ALTERING AGENTS IN ADULTS AND CHILDREN

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The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics Committee on Drugs, and consultants to the Pharmaceutical Manufacturer's Association, has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in humans, and pertain to Phases I through IV of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update as resources permit.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the acquisition of new knowledge these guidelines will require revision.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part, they reflect the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases, other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally acceptable.

Under FDA regulations (21 CFR10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines were initially developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases, the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The Division of Metabolic and Endocrine Drug Products of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

GUIDELINES FOR THE CLINICAL EVALUATION OF LIPID-ALTERING AGENTS IN ADULTS AND CHILDREN

I. INTRODUCTION

A. "General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitious material in each of the specific guidelines.

B. These guidelines pertain primarily to orally absorbable drugs affecting lipid metabolism. While many of the recommendations contained herein are also applicable to non-absorbable agents, sponsors of such products are urged to contact the Division for further guidance. These guidelines do not address requirements for obtaining labelling indications other than lipid-alteration, e.g., the primary or secondary prevention of coronary heart disease, the prevention of stenosis of bypass grafts, the regression of atherosclerosis, etc. The Division hopes to issue a separate draft document in the near future which deals specifically with these issues.

C. The objective of lipid-altering therapy is not merely to alter serum lipids but to diminish the morbidity and mortality from cardiovascular disease and/or pancreatitis that is associated with abnormal serum lipid levels. Our ability to extrapolate the value of any particular lipid-altering drug in accomplishing either of these objectives is limited, however. In clinical trials to date employing coronary efficacy endpoints, the reduction in attributable risk has been moderate. Accordingly, lipid altering agents should be shown to have a relatively low incidence of adverse effects prior to approval for marketing.

D. It is assumed that adequate animal pharmacologic and toxicologic data are available to justify the proposed human studies (see toxicity and teratology guidelines). Sponsors are encouraged to review their pre-clinical development plans with the Division prior to initiation of study protocols.

E. Investigators should be experienced in the performance of clinical trials of new drugs and in the evaluation of lipid-altering drugs.

F. Only patients with primary hyperlipoproteinemia (HLP) should be included in studies evaluating general effectiveness of lipid-altering drugs. Patients with secondary hyperlipoproteinemia should be excluded since results in these individuals may not be suitable for extrapolation to the primary hyperlipoproteinemias, the groups for which the lipid-altering agents are generally intended. The demonstration of efficacy in secondary hyperlipoproteinemias would necessitate special studies.

G. Relevant dietary composition and caloric intake as well as physical activity level should be assessed for each treatment group at baseline and during active therapy. Compliance with diet and medication should be quantified.

H. Laboratory measurements of cholesterol and triglycerides should be standardized as recommended by the Laboratory Standardization Panel of the National Cholesterol Education Program.[1] For multicenter studies, laboratory procedures, particularly for total cholesterol, HDL-cholesterol, and triglycerides, should be uniform.

I. See Appendix II for Guidelines for the Clinical Evaluation of Lipid-altering Agents in Children.

I. PHASE I

A. Study Design

Open label, single-blind, or double-blind designs may be used for initial single-dose tolerance studies and some dose range-finding studies, but placebo controlled, double-blind designs should be used for more prolonged Phase I studies.

B. Study Population

1. Hospitalized or institutionalized adults.

2. Normolipidemic volunteers may be used for single-dose tolerance or short-term, multiple dose tolerance/ pharmacokinetic studies. For other studies, however, subjects should have abnormal serum lipids and, if possible, be classified according to phenotype.

3. Women of childbearing potential, children, and patients with serious diseases, e.g. hematologic, hepatic, renal, or cardiac abnormalities, are to be excluded from Phase I studies. For pharmacokinetic studies, however, inclusion of

[1] N.I.H. Publication No. 90-2964A. February 1990.

women of non-childbearing potential and of elderly patients is encouraged (see also "Guidelines for the Study of Drugs Likely to be Used in the Elderly").

4. Subjects should not have taken other drugs for at least four and preferably six weeks. If the drug previously administered was a lipid-altering agent, it should have been withdrawn for a period of time adequate to bring the serum lipids back to pretreatment levels and to eliminate body stores of residual drug.

C. Conduct of Study

1. All patients should receive a standard diet.

2. Patients should have a carefully performed history and physical examination.

3. Determination of lipid parameters can be made using either serum or plasma samples, as long as consistency is maintained between studies.

4 Safety evaluation should at least include the following:

a. CBC, differential, and platelets
b. P.T. and P.T.T.
c. serum Ca, Na, K, Cl, P, and HCO_3
d. serum total protein, albumin, uric acid, creatinine, BUN, bilirubin (total), and amylase.
e. fasting blood glucose
f. serum T_4 and TSH
g. alkaline phosphatase, SGOT, SGPT
h. urinalysis
i. electrocardiogram (Holter monitoring may be appropriate with certain drugs)

D. Pharmacokinetic studies of absorption, distribution, metabolism, and excretion of the drug, active component, and/or metabolite(s) should be initiated during phase I. Sampling times should reflect the kinetics of metabolites as well as parent drug compound.

I. Phase 2

A. General Comments

1. Phase II trials should be designed to obtain guidance for the design of Phase III trials. They should obtain working estimates of the nature and severity of side effects commonly associated with the new product. They should also include a parallel dose-response study across a number of dose

levels sufficient for the initial characterization of the dose-response curve for the drug.

2. Studies should be double-blind and placebo controlled.

3. Patient history should include information on family history, alcoholic intake, tobacco use, exercise/activity level, and dietary habits.

4. Dietary regimens should be controlled and defined. The National Cholesterol Education Program guidelines may be consulted in this regard.[2] For Types IIa and IIb hyperlipidemia, subjects should follow at a minimum the N.C.E.P. Step I diet (or equivalent) or should continue on a more aggressive regimen if indicated. A constant dietary regimen should be maintained throughout the trial.

For studies in hypertriglyceridemic subjects, including Type V hyperlipidemia, the dietary regimen should in general entail greater total fat restrictions than called for in the N.C.E.P. Step I diet.

5. For study subjects whose lipid values have not stabilized to within the limits specified by the study protocol, the dietary lead-in period may be prolonged.

6. For multiple dose studies with lipid endpoint variables, it is recommended that three pretreatment serum cholesterol and triglyceride values be obtained, preferably at intervals of one to four weeks. It should be recognized, however, that values determined as an outpatient may not accurately reflect the baseline level for a hospitalized patient. Serum lipids should be determined at no shorter than weekly intervals during administration of the drug.

7. In general, it is expected that total cholesterol, total triglycerides, HDL-cholesterol, and calculated LDL-cholesterol levels will be obtained. In addition, drug effects, if any, on apoprotein AI, total apoprotein B, and lipoprotein (a) should be characterized during Phase 2 or Phase 3. In a limited subset of patients, the drug effects on lipoprotein composition should also be assessed by ultracentrifugation and other appropriate methods. For studies affecting HDL metabolism, HDL subfractions and lipoprotein particles should be analyzed by appropriately validated methodology. For patients with chylomicronemia, the chylomicron fraction should be quantitated by centrifugation.

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[2]Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. Arch. Int. Med. 148:36-69, 1988.

The lipid level required for entrance into the study should be specified in the protocol. Lipid entry criteria for pivotal studies should reflect the target population for the drug. For Type IIa and IIb patients, the N.C.E.P. guidelines are an applicable reference. At least 2 and preferable 3 pre-treatment determinations of serum lipids should be made, preferably at intervals of one to four weeks, and the type of HLP determined. Baseline LDL-cholesterol values should be stable prior to including the subject in the test phase of the study. The degree of stability should be stated in the protocol. It is suggested that the difference between the two LDL-cholesterol values preceding active treatment not exceed 12% (of the higher value). It is to be expected that when an arbitrary cutoff value is used for determining hyperlipidemia there will be regression to the mean. This should be taken into account in designing studies and analyzing data.

For studies designed to test drug efficacy in triglyceride reduction, enrollment in most instances should emphasize subjects with Types IV and V hyperlipidemia whose fasting triglyceride levels on dietary treatment average 500-1,500 mg/dl. Adequate numbers of patients with fasting chylomicronemia should be included in each study.

8. General physical examinations before and after therapy should include eye examinations in all patients (general and funduscopic exam and measurement of visual acuity) and slit lamp examinations in an adequate number of patients. Complete ophthalmologic examinations at baseline and on drug therapy (including slit lamp examination) may be required for certain drugs. Refer also to Appendix I for special studies.

B. Early Phase 2

1. Study population: Patients should be ambulatory adults preferably with hyperlipoproteinemia as the sole diagnosis. Women of childbearing potential, pregnant women, or those planning to become pregnant should be excluded. Women of non-childbearing potential and elderly subjects may be included, however (see also "Guidelines for the Study of Drugs Likely to be Used in the Elderly").

2. Although the frequency of visits is determined in part by the number and results of Phase 1 studies and by the chemical nature of the drug, patients should generally be seen weekly for the first two to four weeks and biweekly for another six to eight weeks. Safety laboratory tests and appropriate physical examinations, including body weight, should be done at each visit and serum lipid levels should be determined every two weeks. After three months, patients may be seen at monthly intervals for two to three months and bimonthly thereafter.

C. Later Phase 2

1. The study population may include patients with cardiac or other chronic disease. Provided that all three segments of the animal reproductive studies have been completed and are satisfactory, women of childbearing potential who are using mechanical contraception may be included in the study. Women who are taking oral contraceptives should be excluded because of the known effects of these drugs on serum lipids. Interactions of test drug with other drug therapy may be assessed, e.g., anticoagulants, digitalis, diuretics, beta-blockers, antihypertensives, vasodilators, sedatives, other lipid-altering agents. Subjects receiving beta-blockers, thiazides, or estrogens/progestins may require separate subgroup analyses. With some agents, it may be desirable to study interactions with hepatic mixed function oxidases before drug interactions are studied in man.

2. Blocking (stratification) of patients by type of lipid abnormality, age, sex, race, certain risk factors, or with other diseases prior to randomization will help achieve balance in treatment groups and these subgroups should be analyzed separately when feasible.

3. The frequency of patient visits is generally the same as early Phase 2.

4. Electrocardiograms should be obtained before and after drug administration in all patients.

II. PHASE 3

A. Study Design and Setting

1. The studies assessing efficacy and safety should be prospective, randomized, and double-blind, with parallel test drug and placebo groups. Pivotal studies should specifically include a six-month, placebo-controlled trial with parallel dosing arms representative of the proposed clinical dosing interval in patients with mild to moderate hyperlipidemia (if appropriate, addition of resin may be considered after four months of active treatment). The test drug should also be compared to a reference drug of the same chemical class, if one is marketed. It may also be compared to a reference drug of the same therapeutic class.

Multicenter collaborative trials must have a uniform protocol which includes definitions of how measurements are made and which provides for systematic reporting of data. All study physicians should utilize the same criteria to determine whether a patient is eligible for enrollment and continuation on study therapy.

All decisions to discontinue which are not predefined in the protocol should be mediated by the study monitor before action is taken, except in serious medical emergencies.

Drug and placebo groups should be subdivided further, at least for analysis. Statistical efficiency may be enhanced by stratification prior to randomization into categories such as age, sex, race, extent of lipid abnormality, and selected risk factors.

Should there be more than one type of hyperlipidemia under study, consideration should be given to stratifying and balancing groups with regard to type. In addition, for drugs indicated in Types IIa and IIb hyperlipidemia, efficacy should be characterized separately for heterozygous familial hyperlipidemia and familial combined hyperlipidemia.

Data from open extensions of multicenter trials provides secondary support for claims of safety and effectiveness. For approval of orally absorbable drugs, a minimum experience of 1,500 patients with one year and 500 patients with two years on drug treatment is generally desirable. It is suggested that data from open extensions of placebo or actively controlled studies may be more useful if, for the remainder of the trial, subjects in the control group(s) are switched to a bile-acid binding resin or maintained on active control drug rather than being switched to treatment with test drug.

2. For pivotal studies, patient response should be evaluated after a minimum of 8 weeks on a therapeutic diet before drug therapy is begun. Longer evaluation may be required if lipids and weight do not stabilize within that time.

B. Investigators

1. Investigators for pivotal studies should be experienced in the use of lipid-lowering drugs and willing to participate in a collaborative study.

2. In general, each investigator should study a sufficient number of patients so that the finding of that investigator can be meaningfully evaluated.

C. Study Population

1. The study should include adults (over age 18) with an elevated baseline LDL-cholesterol and/or triglyceride (as defined in section III.A.7.). The criteria for elevation should be specified in the protocol to demonstrate the relationship between the study population and the target population.

2. Pregnant women or those planning to become pregnant should be excluded. Provided that all three segments of the animal reproductive studies have been completed and results are satisfactory, women of childbearing potential who are using an accepted method of contraception may be included in the study. The contraceptive methods should be clearly stated in the protocol and, prior to beginning active treatment, each of these women should have a pregnancy test. A subgroup efficacy analysis should also be done for women using oral contraceptives because of the known effects of these drugs on serum lipids.

3. See Appendix I for a discussion of the factors to be considered in determining the number of patients to be included in the study.

D. Efficacy Evaluation

1. The efficacy evaluation should have the following components:

a. assessment of the extent of lipid alteration, preferably expressed as the mean, median, and range of individual percent changes from baseline to endpoint for each lipid parameter.

b. response rate(s) by degree of baseline lipid abnormality and/or genetic type of lipoprotein disorder, age, sex, race, and concomitant medications, as appropriate.

c. calculated or measured LDL-cholesterol and total serum or LDL-apoprotein B levels should be primary endpoints. Secondary lipid endpoints should include total cholesterol, total triglycerides, HDL-cholesterol, LDL-cholesterol:HDL-cholesterol ratio, and apoprotein AI. Additional data on lipoprotein (a), HDL subfractions and/or HDL particles by immunoprecipitation, and apoprotein E is also desirable in selected phase 3 studies.

1. Descriptions of baseline and endpoint lipid parameters are described in Section III.A.7. During the trial, serum lipids should be determined at least monthly during the first four months and bimonthly thereafter.

2. For absorbable agents, demonstration of at least a 15% reduction from baseline in LDL-cholesterol, in the absence of unfavorable alterations in other lipid parameters, is generally required for drug approval. For non-absorbable agents, a more modest effect may be considered adequate for approval, depending on the safety profile of the drug. If the effectiveness in the treatment of xanthomatosis is also to be claimed, data documenting a reduction in the number and/or a substantial reduction in size of xanthomas compared to a baseline and a concurrent control group must be presented.

E. Safety Evaluation

For multi-year phase III and phase IV studies, it is desirable to consider the appointment of a safety and efficacy monitoring board to review the accumulated data periodically. The board should make recommendations regarding continuation of the study and determine whether changes must be made in the protocol based on safety considerations. A summary of the data reviewed by the board should be sent annually to the FDA. Any recommendations for changes made by the board should be sent promptly to the FDA for review.

1. Safety response categories

a. all deaths (Form FDA 1639, "ADVERSE REACTION REPORT" may be used for reporting purposes)

(1) death due to drug toxicity (specify nature of toxicity)
(2) death due to myocardial infarction
(3) sudden death
(4) death due to other cardiovascular events (specify event)
(5) other deaths (specify)

b. non-fatal events

(1) drug toxicity, definite or suspected (specify)
(2) myocardial infarction
(3) onset or worsening of other cardiovascular conditions such as angina, hypertension, ECG changes from baseline, congestive failure, thrombophlebitis, cardiac arrhythmias, cerebrovascular insufficiency or stroke, peripheral vascular disease
(4) onset or worsening of non-cardiovascular disease such as diabetes, cataracts, hyperuricemia, liver or gallbladder disease, renal disease, coagulopathy, myopathy, etc.

F. Suggested Schedule for Patient Visits

1. Pre-randomization phase

Visit 1 (Screening): Physician describes study and after obtaining informed consent obtains history (including smoking, alcohol intake, and use of other medications or drugs) and basic laboratory tests, including serum lipids.

Visit 2 (two to four weeks later): Ineligible patients excluded; others given complete physical examination and a more complete assessment of cardiovascular risk factors, including activity level; eye examination (see section III.A.8.); ECG. Lipid tests

repeated, current diet assessed and study diet explained. Lipid abnormalities/values in family members should be documented if this information is available.

Visit 3 (two to four weeks from visit 2): Additional diet instruction given and compliance assessed; blood pressure, body weight, and serum lipids repeated. Patients randomized to a treatment group if baseline established.

Visit 4 (two to four weeks from visit 3): Second dietary and lipid assessment (note: dietary lead-in should be a minimum of 6 to 8 weeks).

2. Post-randomization phase

a. Visits should be at least monthly during the first six months and every two months thereafter. Data on dietary compliance and composition should be obtained at least every two months, and drug compliance should be measured. Appropriate laboratory safety tests should be performed at months 1, 2, 4, and 6 and periodically thereafter.

b. Every six months: an abbreviated history and physical examination.

c. Every twelve months: complete reevaluation with detailed history and physical examination, including eye and ECG examinations. Particular attention should be given to the assessment of cardiovascular status.

3. Missed visits: If a regular visit is missed, the patient should be contacted by phone and a new appointment made as soon as possible and preferably within 14 days of the original appointment.

4. If the patient moves to a new location, but one where another collaborating investigator is following the same protocol, an effort should be made to continue the patient in the same program. If no such investigator is available, the patient should be discontinued from the study.

5. Dropouts: An attempt should be made by the sponsor to contact the patient or his/her physician to determine health status at least every six months for the duration of the study.

G. Statistical Analysis

At the end of the trial the primary statistical analysis should assess the magnitude and the sustainability of the change in LDL-cholesterol, HDL-cholesterol, triglycerides, and apoproteins within each treatment group and for each diagnostic category (type of hyperlipoproteinemia, presence or absence of other factors of prognostic importance). For placebo-controlled trials, the mean and median of percent change from baseline for each patient in the control group relative to the drug-treated group(s) should be compared and the statistical hypotheses which have been defined prior to developing the sample size should be tested. For positively controlled trials, the ninety-five percent (95%) confidence intervals should be calculated and presented for each timepoint analyzed. An additional covariate analysis, taking into account the effects of diagnostic category, age, sex, race, relative weight, blood pressure, smoking and alcohol use, presence or absence of diabetes, center and investigator, duration of therapy, baseline lipid levels, and other appropriate interactions, is also generally appropriate. Efficacy should be presented as relative frequency histograms and/or scattergrams, as appropriate, for each subgroup. In some instances, interrelationships between efficacy and baseline level of the same or other lipoprotein fraction(s) may be analyzed, e.g., magnitude of LDL-cholesterol change as a function of baseline LDL level.

Similar analyses should be made for adverse reactions and unexpected events, and for selected clinical and laboratory findings. Hazard rates should be analyzed as a function of treatment group, dose, duration of therapy, age, sex, and other baseline characteristics. In addition to analyzing pooled data, these analyses should be done separately for each investigator.

Statistical analyses should employ both an intention-to-treat approach and additional analyses excluding patients with missing data for the timepoints and parameters being considered. An analysis by degree of dietary and drug compliance should also be performed.

III. SUGGESTED SPECIAL STUDIES

A. Studies to Elucidate Mechanism or Mode of Action

1. Lipoprotein turnover rates and total exchangeable lipoprotein pool.

2. Lipoprotein receptor activity, rates of receptor and non-receptor medicated lipoprotein uptake.

3. Tests of clotting, platelet function.

4. Effect on atherogenesis in animal test models.

B. Studies in Special Populations

1. Children (guidelines in Appendix II)

C. Special Safety Tests

2. Liver biopsies in patients undergoing elective abdominal surgery.

3. Studies to determine lithogenicity of bile in patients on the lipid-altering drug of interest.

4. Gallbladder ultrasonography before and after chronic dosing with agents known or suspected to increase gallbladder disease or bile lithogenicity.

APPENDIX I

Sample Size

The exact sample size must be computed by the sponsor using the following considerations plus any additional factors which are indicated by the claims for the product:

a. The objectives of the trial and the specific endpoint variables.

b. The length of the study.

c. Patient characteristics which may affect the study outcomes.

d. The comparisons (statistical hypotheses) which are to be tested at the end of the study.

e. The expected event rates in the drug group and the placebo group.

f. The size of the phenomenon or the difference between event rates to be detected; the difference between the average lipid change from baseline in patients in the study drug and reference groups; the percentage of cases in the study drug and reference groups who may be expected to achieve the desired amount of lipid alteration, etc.

g. The expected variance in the primary endpoint measurement (this should also be justified).

h. The probability of detecting in the study sample a phenomenon which is present in the population, i.e., the power of the proposed tests (1 minus beta, etc.), based upon each essential event.

i. The proposed level for testing statistical significance (alpha error) for each event used in a to c above. This should take frequency of interim analyses into account.

j. The dropout rates which are expected in the study drug and reference groups during the study.

APPENDIX II: GUIDELINES FOR THE CLINICAL EVALUATION OF LIPID-ALTERING AGENTS IN CHILDREN

I. General

There is evidence to suggest that in many cases the atherogenic process leading to sever cardiovascular disease in adult patient has its origins during childhood. Difficulty in demonstrating clinical effectiveness (i.e., reduction in coronary artery disease) of hypolipidemic agents in adults may be partially due to the fact that therapy is started too late. Therefore, it may be reasonable to attempt to control these factors during childhood in high-risk individuals.

The FDA has published General Guidelines for the Evaluation of Drugs in Infants and Children. The investigation of lipid-altering agents in children should meet these general guidelines.

Additional comments need to be made with regard to investigating lipid-altering drugs in children since the proposed therapy is different in many ways from other drug evaluations in young subjects. These drugs are administered to apparently healthy children in the hope of preventing disease later in life. One great concern about the use of lipid-altering drugs in children is related to the possibly unique needs of children for lipids in the growth and development of the central nervous system and other body structures. Since the site and/or extent of action of some of the lipid-altering drugs is not known, it cannot be predicted with certainty that serious side effects will not occur. In addition, the drug therapy will extend over many years and will be carried out during periods of very rapid growth and development. Finally, in this age group, it is not certain that the pharmacologic effect that is anticipated (alteration in serum lipids) will result in a decrease in the rate of development of atherosclerosis.

II. Study Population

A. Children with hyperlipidemias should be identified early by pediatricians. Some children may be identified because they have a family history of early death due to atherosclerotic cardiovascular disease. After children with elevated serum lipids are identified, they should be properly classified as to the lipoprotein abnormality present and whether this represents primary or secondary hyperlipidemia. Patients with secondary hyperlipidemia (due to dietary abnormalities, nephrotic syndrome, hypothyroidism, etc.) should not be considered for lipid-altering drug therapy.

B. Initial studies should include only those children who appear to be at greatest risk, based upon personal history, family history, physical and laboratory findings. Children with documented familial heterozygous or homozygous hypercholesterolemia not responding adequately to diet meet this requirement.

C. Patients with a primary hyperlipidemia should enter a program of dietary control before being considered eligible for drug therapy. An adequate trial (4-6 months) of diet therapy should always precede the institution of a drug in children. If after meeting the requirement of greatest risk and after careful dietary regulation the abnormally elevated serum lipids do not approach the normal range, the child may be entered into a study of the clinical effectiveness and safety of a hypolipidemic agent. In general, a minimum LDL-cholesterol value of 190 mg/dl on dietary therapy should be required. HDL levels may also be considered in identifying higher risk patients.

D. Although the potential benefits of early treatment should not be denied patients who are at greatest risk, it is unlikely that children with heterozygous familial hypercholesterolemia below five years of age will be accepted for drug therapy.

III. Drug Studies to be Carried Out Prior to Initiation of Studies in Children

A. Each of these agents must have been submitted to extensive evaluation in developing animals. It should be clear that the agent causes no alteration in physical development, central nervous system function, or eventual reproductive potential.

B. Before investigating lipid-altering agents in children there must be some understanding of the mechanism of action of the drug. Although the molecular mechanism might not be known, there must be a greater understanding that a simple cause and effect relationship. In order to outline physiologic parameters that need to be monitored while evaluating a particular drug, some information regarding the mechanism of the drug's action must be available.

C. Reasonably extensive evaluation of the safety and effectiveness of the drug in adults should have been undertaken before pediatric investigations are started. The data in adults should provide guidance as to dose, response, duration of action, and physiological disposition of the drug.

IV. Protocol

A. Individual protocols should be developed for a specific drug based upon the pharmacology of the agent.

B. The children enrolled in these studies should be assigned to the appropriate age groups: childhood, pre-adolescent, adolescent. Depending on the drug, studies might first be done in adolescents before pre-adolescent children are exposed. After drug therapy is started, a sufficient number of subjects from each of these groups should be thoroughly evaluated for absorption, distribution, metabolism and excretion of the drug. Therefore, good methods of drug assay must be available. Kinetic measurements should be made at steady state for the test drug.

C. After there have been some years of experience with a particular agent, and the data show both a favorable alteration in serum lipids in a significant number of the study patients and acceptable safety, additional children may be studied--for example, children diagnosed as having a hyperlipidemia but whose risk of early coronary artery disease is not as great.