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DIETARY INTERVENTION STUDY IN CHILDREN
PROTOCOL

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CHAPTER 1

BACKGROUND AND REVIEW OF LITERATURE

1.1 Introduction

Despite the recent decline in the United States coronary heart disease (CHD) death rate,¹ it remains the most common cause of premature death and disability in this country, often developing in people during their most productive years. Two out of three CHD deaths occur outside the hospital, and 20% present with sudden death as the first, last, and only symptom.² CHD accounts for more than 550,000 deaths per year in the United States (28.5% of all deaths), and the heart disease rate has been at a substantial level for the last 35 years.³ The hospital costs CHD incurs are among the highest of any disease,⁴ with a total economic cost in 1979 estimated at thirty-eight billion dollars.⁵

Few well conducted clinical trials have considered the relationships between diet, human development, and atherosclerosis. The purpose of the Dietary Intervention Study in Children is to investigate the feasibility, safety, and efficacy of dietary intervention in prepubescent and pubescent children with elevated low density lipoprotein cholesterol (LDL-C). A safe, acceptable and efficacious LDL-C lowering diet has implications for the diet and education of children in schools, in pediatric practices, in public health programs and even in mass media campaigns to establish for subsequent generations both healthy eating habits and healthy circulatory systems which will reduce the nation's burden of cardiovascular disease mortality and morbidity.

1.2 Development of Atherosclerosis During Childhood1.2.1 Fatty Streaks

In a study of autopsied children in New Orleans, all children over three years of age had sudanophilic intimal deposits in the abdominal aorta.⁶ Fatty streaks were present in every aorta and in more than 70% of the coronary arteries by age 15. Nearly half the white males and black females had coronary artery raised lesions by age 20-24.⁷ The fibrous plaques increased in number and in size until the fourth decade when the prevalence ranged from 36-80%. Aortic fatty streaking is so prevalent in humans that it is impractical to compare different populations.⁷ Antemortem cardiovascular disease risk factor levels in 35 youngsters of Bogalusa, Louisiana,⁸ have been studied in relation to early atherosclerotic lesions in the aorta and coronary arteries (mean age at death = 18 years). Independent of race, sex, and age, aortic fatty streaks are strongly related to prior levels of both plasma total cholesterol (TC) and LDL cholesterol (LDL-C) ($r = 0.67$, $p < 0.0001$ for each association), and are inversely associated with the ratio of HDL-C/(LDL-C + VLDL-C) ($r = -0.35$, $p = 0.06$). Coronary artery fatty streaks are associated with increasing VLDL-C levels ($r = 0.41$, $p = 0.04$).

1.2.2 Fibrous Plaque Development

The tenet that atherosclerosis begins early in life has been discussed and reviewed by several researchers.⁹⁻¹⁴ Pathologic studies of the coronary arteries of young men in World War II and in the Korean and Vietnam conflicts have all provided convincing evidence of coronary fatty streaks and raised coronary lesions (fibrous plaque) in young adults.¹⁵⁻¹⁷ Fatty streaks in the coronary arteries, while rarer before the age of ten, are quite frequent in the second decade and nearly always present after the age of 20 years.¹⁸ The relation between fatty streaks and the more advanced raised intimal lesion (fibrous plaque) in coronary arteries has also been investigated from 4,737 autopsied cases of both sexes, ages 10-39 years, from six locations and race groups in the International

Atherosclerosis Project.⁷ The microscopic findings are consistent with a gradual transition from coronary fatty streaks to fibrous plaques, a process in cases that began before age 20 years and increased rapidly in the two decades following. The coronary artery fatty streaks in childhood predicted the advanced atherosclerotic lesions in middle-age, since populations with extensive fatty streaks in childhood tended to have more extensive raised atherosclerotic lesions in middle age.⁷

1.2.3 Cholesterol and Lipids

Average levels of serum cholesterol in pediatric populations of countries with significantly lower coronary heart disease (CHD) incidence rate are at lower values when compared with those from countries with higher CHD rates.¹⁹ These differences are noted after the first year of life; cord blood levels appear to be similar cross-culturally with means in the range of 65-75 mg/dl.¹⁹ It was further noted in Bogalusa that within populations children with the lowest levels of serum TC consumed significantly less dietary fat than children in the upper percentiles.²⁰ These facts, along with the information available on adults, lead to the conclusion that reduction of TC and LDL-C in children may reduce long-term risk of CHD. Further, effective inculcation of heart healthy eating habits may be best achieved during childhood.

1.2.4 Relationship of Childhood Lipoprotein Levels to Adult Disease

There are presently no longitudinal data available for determining if hypercholesterolemia during childhood places an individual at increased risk for CHD. However, there is extensive indirect evidence of such a relationship. There is significant tracking of LDL-C levels during childhood in Bogalusa.²¹ Children with hypercholesterolemia have more male relatives, particularly fathers, with hypercholesterolemia and increased CHD mortality.²²⁻²³ Both male and female relatives of the hypercholesterolemic children have three to five times the

frequency of deaths from myocardial infarction (MI) as relatives of children in the lowest tertile. Particularly increased is CHD risk in the hypercholesterolemic relatives of the hypercholesterolemic probands.²⁴ At all ages after age 30, the relatives with the high LDL-C had up to eight to ten times the risk of developing CHD as the relatives with normal LDL-C.

In the Bogalusa Heart Study, children with a history of paternal MI had higher levels of apoprotein B (apoB) and lower levels of apoA-I. The apoproteins were better discriminators of increased risk of paternal MI than were the lipoprotein cholesterol levels. Children with high levels of LDL as assessed by apoB or cholesterol are likely to be at increased risk for atherosclerotic vascular disease in their adult years. This supports attempts at intervention to lower LDL in childhood, particularly for those at risk with high LDL levels.

Epidemiologic evidence indicates that children whose lipid and lipoprotein levels place them in the 95th percentile of the distribution are potentially at the highest risk for future coronary heart disease.²⁵⁻²⁸ While other factors are known to accelerate the development of severe atherosclerotic plaques, the level of blood cholesterol, specifically LDL-C, plays a critical role in atherogenesis and correlates strongly with incidence of CHD.

1.3 Genetic Versus Cultural Determinants of Increased LDL Levels

The average level and range of plasma cholesterol in American children, where there is a high incidence of adult CHD, is considerably higher than those in children from populations where the incidence of adult CHD is low.²⁹ Serum total and HDL cholesterol concentrations in 560 boys, aged seven and eight years was studied in 16 countries from various regions of the world, selected on the basis of having different patterns of diet and different rates of mortality from CHD.³⁰ The serum total cholesterol concentrations were the lowest in three West African

countries and in Pakistan, with intermediate values in the Philippines, Greece, Portugal and Hungary. The highest levels were found in the boys from the remaining European countries and the United States where the prevalence of CHD is the highest.

Within populations of American children, the correlations between the dietary content of cholesterol, total fat, saturated fat and polyunsaturated fat and the plasma levels of lipids and lipoproteins, as judged by 24-hour dietary recalls, are generally statistically significant but of low magnitude.³¹⁻³² This may be due, in part, to inherent difficulties with the method of collecting dietary data, and to the fact that intraindividual variation will bias estimates of correlation toward zero and will result in misclassification of subjects into ranges of usual dietary intakes.³³ The fact that differences between diet and plasma levels of cholesterol in various countries are so great compared to differences within a single country, is likely to be related to large inter-country differences in dietary habits, in contrast to small intra-country differences. For example, when children from the 16 countries were studied,³⁰ there was a high correlation ($r = 0.91$) between the mean serum cholesterol levels and the availability of animal products in 1973/1974 per capita, expressed as a percentage of total energy supplies.

In the LRC population studies, 32% of the first degree relatives of children with top decline LDL-C also had top decile LDL-C³⁴⁻³⁵ (see Footnote 1 found at end of chapter). For whites, 27% of the first degree relatives of hypertriglyceridemic probands had top decile LDL-C.³⁶ With LDL-C, there were significant mother-pediatric progeny and father-pediatric progeny correlations of approximately 0.4. These investigators estimated that genetic heritability of LDL-C level of 0.62 as compared to environmental heritability of 0.7. This suggests a significant contribution of genetic heritability and a relatively

marginal environmental contribution. However, the degree to which familial associations of risk factors arise from shared heredity and shared environment (lifestyles) is conditional on the range of variation of the environmental factors in a given population and its families. When lifestyles are fairly uniform the relative contribution of genetic factors will inevitably be greater. These studies demonstrate significant familial aggregation and indicate that it would be valuable therefore to intervene in families since other family members are likely to have high LDL. However, the numerous assumptions in this type of analysis do not permit a valid separation of environmental and genetic causes of increased LDL-C.³⁷

1.3.1 Known Genetic Conditions

1.3.1.1 Familial Hypercholesterolemia

Increased LDL-C can be caused by single gene defects. Familial hypercholesterolemia (FH) is a monogenic disorder with elevated LDL-C caused by a deficient number of functional cell surface LDL receptors³⁸ (Footnote 2). Estimates of the prevalence of heterozygous FH is approximately 4 to 14% of hypercholesterolemic subjects³⁴⁻³⁶ and 1:500 to 1:200³⁹ of the general population.

1.3.1.2 Familial Combined Hyperlipidemia

Another monogenic condition associated in some individuals with increased LDL-C is familial combined hyperlipidemia. The estimated prevalence is 1.0-1.8%.⁴⁰⁻⁴² One gene may have pleiotropic phenotypic expression with subjects having high VLDL alone, high LDL alone, or both high VLDL and LDL. There appears to be considerable overlap between this disorder and the hyperapobeta-lipoproteinemia described by Sniderman⁴³⁻⁴⁴ (Footnote 3). In both, an increase in apoB appears to be the more consistent lipoprotein abnormality. Subjects with these disorders appear to be characterized by increased production of apoB containing

lipoproteins. LDL apoB is high in one-third of children of men who have had an MI and have increased LDL apoB.⁴⁵ Although this is compatible with a monogenic trait, a careful genetic analysis was not reported. Additionally, 27% of the affected children had HDL-C below the fifth percentile of children of the same age and sex.⁴⁵ This abundance suggests an interrelationship between LDL and HDL, but the metabolic basis has not been defined. It will be interesting to observe whether an intervention that is associated with a decrease in apoB is associated with an increase in HDL-C and apoA-I.

1.3.1.3 Hyperapobetalipoproteinemia

Hyperapobetalipoproteinemia (hyperapoB) is a lipoprotein phenotype characterized by a significantly elevated plasma level of the major apoprotein of LDL, apoB; the level of LDL-C is within the normal range or mildly elevated.^{43,46-47} HyperapoB is due to the presence of an increased number of LDL particles that are smaller and denser with a low ratio of LDL-C to LDL apoB.⁴⁸ One-third of children (mean age 15 years, range 3-21 years), who were born to a parent who had both hyperapoB and premature CHD (before age 55 years), were also found to have hyperapoB.⁴⁹ In some families, the phenotype of hyperapoB may reflect the expression of familial combined hyperlipidemia (FCH), a dominant disorder that can be expressed as multiple lipoprotein phenotypes (types IV, IIa, and IIb) and that is prevalent in survivors of myocardial infarction.^{42,50}

1.3.1.4 Summary of Genetic Conditions

The low frequency of the monogenic disorders suggests that the majority of individuals with high LDL arises from environmental and less obvious polygenic factors. Sing has estimated that the variability in serum cholesterol in the U.S. is determined half by genetic factors and half by environmental factors.⁵¹ Thus

there is likely an interaction of genetic and environmental factors in many individuals that contributes to increased LDL.

1.3.2 Endogenous and Exogenous Determinants of Plasma Lipids in Youngsters

The population of interest is boys and girls between the ages of eight and ten years, a period of pre-adolescence. The levels of plasma TC and LDL-C are reasonably comparable between the boys and the girls at this age as are the HDL-C levels. However, in adolescence there is a temporary fall in the plasma TC level.⁵²⁻⁵³ In addition, HDL-C levels begin to fall in males but remain relatively constant in females during this period.^{25,52} It is therefore important to consider this fluctuation when the effect of therapeutic intervention is under study in subjects of this age.

The onset of puberty apparently has opposite effects on LDL-C levels between boys and girls. In the LRC prevalence study, mean LDL-C for boys six to ten years was 92.5 and for boys 11 to 15 years was 96.5. For girls the mean LDL-C level was 100.0 in the younger girls and 97.3 in the older girls.⁵⁴ Some of this confounding effect will be moderated by randomization, but it is critical that maturation rates be carefully monitored to assure that there are not biasing differences in maturation rate between study and control groups. Furthermore, differences in maturation at the end of the observation period need to be carefully assessed to assure that the dietary intervention does not retard maturation among intervention group children.

1.3.2.1 Endogenous Hormones

Considerable attention has been focused upon the adolescent period to examine possible influences of endogenous hormones as an explanation for the adverse lipoprotein profile that develops in males. Plasma LDL-C and HDL-C levels

are not apparently simply related to endogenous testosterone levels. These interrelationships are complex and significantly influenced by both the estradiol levels and Quetelet index.⁵⁵

1.3.2.2 Exogenous Hormones

In the Lipid Research Clinic (LRC) population, the use of oral contraceptives in adolescent girls was associated with a threefold increase in hypercholesterolemia and a fivefold increase in hypertriglyceridemia.⁵⁶ Another group found a significantly higher plasma TC level and a trend towards a higher triglyceride level but lower HDL-C level in users than in non-users.⁵⁷ Consequently, it is important to consider the effect of exogenous hormones on plasma lipid levels in a longitudinal long-term clinical trial that will eventually include adolescent girls in the study population.

1.3.2.3 Smoking

Cigarette smoking in adolescents has been shown previously to lower the level of HDL-C and increase the ratio of LDL-C to HDL-C.⁵⁷⁻⁶⁰ While most if not all of the children originally ascertained to this study between the ages of eight and ten years will be nonsmokers, it will be important to monitor the possible initiation of cigarette smoking in the study population.

1.3.2.4 Obesity

Obesity in childhood can be associated with higher plasma levels of TC, total triglycerides (TG), LDL-C and VLDL-C, but lower levels of HDL-C.⁶¹ Such obese children, on intervention, often require the prescription of hypocaloric diets which can produce a temporary reduction in the growth curve of such individuals,⁶² although such is not always the case.⁶³ There have also been

problems in meeting the calcium and iron RDAs in children on weight-reduction diets.⁶⁴

1.4 Efficacy of Diet to Decrease LDL

Serum cholesterol is lowered in adults by reduced intake of saturated fatty acids (SFA) and cholesterol, increased intake of polyunsaturated fatty acids (PUFA), loss of body fat, to a small extent dietary fiber (particularly pectin and other water soluble fibers), and possibly by vegetable protein.⁶⁵ Less information is available in children particularly related to dietary effects on lipoprotein, lipid, and apoprotein levels. Moderate dietary changes in institutionalized adolescent boarding school males was modified by decreasing mean daily intake of cholesterol from 544 to 300 mg, total dietary fat from 39% to 33% of calories, saturated fat from 15% to 10% of calories and by increasing the ratio of polyunsaturated to saturated fat from 0.2 to 1.0; the average baseline blood cholesterol level of 178 mg/dl was promptly lowered by 15%, and returned to baseline upon resumption of ad lib diets.⁶⁶ These results, however, do not relate to the feasibility of dietary alterations in free-living households.

1.4.1 Studies of Free-Living Populations

Diets which reduce plasma cholesterol and LDL-cholesterol have been applied in a relatively controlled secondary school setting,⁶⁷⁻⁶⁸ and in a less controlled elementary school setting.⁶⁹ While diets restricted in cholesterol, total fat and saturated fat will lower the plasma TC level in most free-living children, the response is often variable. As two experienced researchers in the dietary treatment of hyperlipidemias have written, "Even well-motivated patients do not make abrupt changes in their dietary habits. It may take many months and even years to make permanent changes in patterns of food consumption."⁷⁰

In general, children with a higher initial plasma cholesterol level show the most response, while those with a lower cholesterol level show less of a response.⁷¹⁻⁷² A community intervention⁷³ succeeded by reducing the percent of calories from fat from 37% to 32%, and by increasing the ratio of polyunsaturated to saturated fat from 0.13 to 0.6, in 13-15 year old children in North Karelia, Finland. After two years, their baseline mean plasma cholesterol level (197 mg/dl) had fallen about 10%.

In the United States, the American Heart Association, through its Committee on Heart Health Education in the Young, has developed and promulgated a number of educational programs for school age children.⁷⁴ In addition, the "Know Your Body" program, a study conducted by the American Heart Foundation,⁷⁵ has achieved a four to six percent net difference in mean cholesterol levels between schools in which they intervene and control schools. Finally, an interactive model of intervention on hypertension developing a total community approach (ADAPT)⁷⁶ has been attempted.

Although the model was designed for hypertension prevention, it is applicable for all cardiovascular risk factor intervention, including blood lipids.

1.4.2 Dietary Intervention in Familial Hypercholesterolemia

A number of studies have shown that the plasma TC and LDL-C levels in heterozygous FH children can be reduced on the average of 10-15% through dietary measures alone⁷⁷ (Footnote 4). The feasibility and efficacy of dietary alteration in free-living children with heterozygous FH, and in free-living normal children has been examined.⁷⁸ Consumption for three months of a diet with a P/S ratio of 1.5 and total fat less than 35% of calories was associated with 11 and 9 mg/dl decreases respectively in TC and LDL-C even when dietary cholesterol exceeded 450 mg/day. Plasma LDL-C was lowered for sustained periods without decreasing HDL-C.

In the FH subjects, further 10 mg/dl reductions of TC and LDL-C occurred when

dietary cholesterol was reduced to less than 160 mg per day. Fernandes⁷⁹ compared vegetarian diets with 11 mg of cholesterol per day vs 109 mg per day with no change in total fat but an increase of P/S from 1.3 to 1.83 in children with FH. There was 10% decrease in RC, LDL-C, and apoB and a 4% decrease in apoA-I. The difference in the P/S ratio could account for 25% of the decrease using the Keys Formula.⁸⁰ Since there was no change in LDL-C/total apoB, this suggests a possible decrease in the number of LDL particles; but the LDL apoB was not measured. Taken together these studies indicate the efficacy of diet to decrease LDL levels selectively. The subject in both trials had FH and their motivation for dietary adherence may be affected by a prominent family history of CHD. Additionally, the response to diet of the children with FH may differ from individuals with other causes of increased LDL-C.⁸¹

1.4.3 Diet and Fatty Acid Saturation

Several recent studies of cholesterol lowering diets in adults and a recent review⁸² suggest caution with high intakes of dietary PUFA or carbohydrate. A diet rich in monounsaturated fats (MUFA), a diet low in fat (20% fat calories), and a diet high in SFA have been compared.⁸³ Both the high MUFA and low fat diets lowered TC (by 13% and 8%) and LDL-C (by 21% and 15%). However, the low fat diet raised TG and reduced HDL-C compared to the high SFA or MUFA diets. Thus the LDL-C/HDL-C ratio was significantly lower with the high MUFA than with the low fat diet. An isocaloric substitution of MUFA for PUFA in normotriglyceridemic subjects was associated with an equivalent lowering LDL-C.⁸⁴⁻⁸⁵ High carbohydrate diets may produce a transient increase in VLDL triglycerides and decrease in HDL-C.⁸⁶ In free-living hypercholesterolemic adults a diet consistent with Phase I of the AHA diet that decreased total fat, increased carbohydrate, and decreased cholesterol, lowered TC 13% and LDL-C 19%. However, this was associated with

decreases in HDL-C of 10%, HDL₂-C of 13%, and apoA-I 17%. There was no significant correlation between the decrease in LDL-C and the decrease in HDL₂-C.

This suggests that a high carbohydrate diet may lower HDL₂-C more than LDL-C in some individuals.⁸⁷ These studies suggest caution with high PUFA or high carbohydrate intakes. There are likely to be significant quantitative and qualitative variations in the responses of individuals to a dietary intervention.

Assessment of dietary intervention from food records can be based on formulas relating saturated to polyunsaturated fatty acid, and cholesterol content. This lipid effect can be expressed as the quantity B where $B = 0.475 (\text{SFA} - 0.5 \text{ PFA}) + 0.2 \text{ cholesterol}$ and fatty acids are expressed in grams while cholesterol is expressed in milligrams.⁸⁸

1.4.4 Physiological Determinants and Possible Mechanisms of Modified Diet

A diet modified in cholesterol, total fat, saturated fat and polyunsaturated fat may lower plasma TC and LDL-C levels by decreasing lipoprotein synthesis or enhancing plasma LDL catabolism, or both. Reductions in LDL concentration during a low fat (25% of calories) diet are largely explained by diminished synthesis and possibly also by increased fractional catabolic rate of LDL.⁸⁹ A diet enriched in polyunsaturated fatty acids decreases synthesis of both VLDL apoB and LDL apoB.⁸⁹

High levels of dietary cholesterol in humans down-regulate LDL receptor activity in mononuclear cells by about 40%, a decrease that is inversely correlated ($r = -0.80$) with the 11% rise in LDL cholesterol level.⁹⁰ Conversely, a diet low in cholesterol may increase the activity of LDL receptors in the liver, producing enhanced uptake and catabolism of LDL through the LDL receptor pathway.⁹¹⁻⁹² The investigation of the increment in TC with cholesterol feeding and the derepressed LDL receptor activity in cultured mononuclear cells at baseline⁹³

has revealed a strong inverse correlation ($r = -0.74$). The increase in LDL-C with dietary cholesterol has been observed to be inversely related to the percent change in the expressed LDL receptor activity, i.e., the individuals who had the greatest range of suppressible LDL receptor activity had the least increase in LDL-C.⁹⁰ These studies suggest that individuals with a high capacity for LDL receptor activity producing hyperresponse to dietary cholesterol may account for a significant fraction of the individuals who have high LDL-C. These individuals may be very responsive to restriction of dietary cholesterol. The consistency and determinants of response to SFA, PUFA, and carbohydrate have not been examined.

The response of serum cholesterol to dietary cholesterol in humans is at least partially reproducible and stable over a prolonged period. Sixteen percent of the population would have a responsiveness to dietary cholesterol of more than 150% of the mean.⁹⁴ It is estimated that 9% of random subjects would be hyperresponders.⁹⁵ The mechanisms that determine dietary response were not defined in these studies.

1.5 Actual Known Childhood Diet

Nutrient intakes and dietary patterns of 871 ten year old children have been examined by 24-hr dietary recalls.⁹⁶ Cohorts were examined in Year 1 (1976-77), Year 4, Year 6, and Year 9. Snacks represent roughly one-third of daily energy intake, yielding one-fifth of the day's protein, one-third of the fat, and two-fifths of the total carbohydrate intake. Breakfast contributed only 10 to 15% of daily energy and major nutrients with lunch and dinner each contributing 20 to 30% of the total daily intake. This suggests that snacks are an important area for dietary intervention to decrease fat intake.

Raw energy intakes were lower in Year 9 than in Year 4 ($p < 0.05$), and energy intake per kg was lower in Year 9 than in earlier surveys. This is associated with increased weight for height among the ten year olds. This suggests that physical activity has decreased. There were not detectable racial differences but boys has higher intakes than girls (mean = 67 vs 57 kcal/kg, $p > 0.0001$). The higher intake per kg body weight for boys were equally distributed for protein, fat, and carbohydrate.

There were no significant year-to-year differences for total protein, fat, and carbohydrate as percentages of kilocalories. Mean protein density of the diet for all children was consistent over time, varying only from 13.0 to 13.5% of calories. Whites had greater intakes than blacks (mean 13.4 vs 13.8, $p < 0.05$). Boys had greater intakes than girls (mean = 13.6 vs 12.8%, $p < 0.005$). Two-thirds of the protein came from animal sources and one-third from vegetable sources. Mean fat intake contributed 38% of energy intake without difference as to sex or race; with 10th, 50th, and 90th percentiles of 28, 38, and 48%. One-half of total energy intake came from carbohydrate without race differences, but girls had greater intakes than boys (mean = 50.7 vs 49.1%, $p < 0.02$). The 10th, 50th, and 90th percentiles were 37, 50, and 62%, respectively. Starch intake provided one-third

of the total carbohydrate. Sucrose comprises 18.5% of energy intake. Whites have a higher sucrose intake than blacks. This is reflected in a sucrose/starch ratio of 1.39 in whites compared to 1.08 in blacks. Whites have a lower intake of fiber (2.48 gms) than blacks.

Saturated fatty acid (SFA) intakes were lower in Year 9 than in earlier surveys ($p < 0.05$), but unsaturated fatty acid (USFA) intakes were not different.

Polyunsaturated fatty acid (PUFA) intakes were lower in Year 1 than in subsequent surveys ($p < 0.05$). SFA, USFA, and PUFA intakes were without sex or racial difference. Mean dietary cholesterol intake was 324 mg in Year 1, 322 mg in Year 4, 317 in Year 6, and 266 mg in Year 9. The proportion of children with intakes greater than 300 mg ranged from 28% (Year 9) to 42% (Year 1). SFA provided 14 to 16% of daily energy intake. Median P/S ratios were 0.29, 0.37, 0.45, and 0.44 for Years 1-9 respectively, while 90th percentiles were 0.53, 0.68, 0.85, and 0.83.

Comparison of the combined dietary surveys of Bogalusa children with the American Heart Association (AHA) Phase 1 diet reveals that about 14% of children met the total fat recommendation of no more than 30% fat, and this did not change over time. In Year 1 of survey no child met the P/S recommendation, and only one child did so in Year 4 of survey. In Years 6 and 9 of the survey, 7% and 5%, respectively, and P/S ratios greater than 1. In Year 9 there was a noticeable improvement in the percentage of children meeting the dietary cholesterol goal, but many children still exceeded the recommendations. In Bogalusa, sucrose contributed 18% of total calories compared to the dietary goal of 10%.

1.6 Official Views

The National Institutes of Health Consensus Conference on Lowering Blood Cholesterol to Prevent Heart Disease recommended, "It is desirable to begin prevention in childhood because patterns of life style are developed in childhood.

The moderate-fat and moderate cholesterol diet, recommended for the population at large in this report should be suitable for all family members, including healthy children over the age of two years."⁹⁷ This statement has met with some skepticism and opposition⁹⁸ which takes its roots in unanswered questions on the diet changes necessary to reduce atherosclerosis in the United States, the safety of restricted diets for young children, and the best diets for preventing atherosclerosis. Because of lack of information on the safety of restricted diets, the American Academy of Pediatrics voiced responsible opposition to extending the American Heart Association's "prudent diet" to young children.⁹⁹

The slowness of the community of United States pediatricians in agreeing to an aggressive approach is reflected in the statement of a Consensus Conference attendee (Alvin Mauer): "The Consensus Conference, in my mind, resolved no issues regarding diets to be recommended during childhood and adolescence. Data are urgently needed to assess the effects of restricting fat and cholesterol and of increasing the proportion of polyunsaturated fats on the growth and health of individuals during the first two decades of life.

One feature of the criticism presented⁹⁸ was that the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) diet which "derived 35% of its calories from fat, had a polyunsaturated-to-saturated fat (P/S) ratio of 0.8, and supplied less than 400 mg/day of cholesterol ... was effective in reducing plasma cholesterol levels by only about 5%." However, it must be noted that the dietary regimen used in the LRC-CPPT was not designed to achieve more than a 5% reduction in plasma cholesterol. Among various diets which could be considered as

alternatives to the LRC-CPPT diet are the American Heart Association diet for Americans, vegetarian diets, fish oil-rich diets, fiber-rich diets, and complex carbohydrate-rich diets.

The American Academy of Pediatrics Committee on Nutrition in recent publication¹⁰⁰ would only recommend dietary intervention for serum cholesterol levels above the 95th percentile. Furthermore they deemed the optimal fat intake to be indeterminant, but stated that "30% to 40% of calories seemed sensible for adequate growth and development." This position is somewhat divergent from views existing in the American Heart Association.

1.7 Safety of Diet

In a recent LRC Program survey of 17 year olds in Jerusalem, the percent of calories from fat was 33.7% in Israeli males and 35.2% in Israeli females, with a P/S ratio of 0.86 and 0.84, respectively.¹⁰¹ Cholesterol intake (mg/1,000 kcal) was 181 mg for males and 194.9 for females. These intakes were compared with those in United States 17 years olds, in whom 42.2% of the total kcal was from fat, the P/S ratio was 0.43 and the cholesterol intake was 151.9 mg/1,000 kcal.¹⁰¹

The consumption of such a diet in Israel was not associated with changes in growth in the preceding adolescent period. Average heights (cms) of Israeli males (172.8) and females (162.3) were similar to 15-19 year old American males (173.4) and females (162.8).

A long-term diet in children heterozygous for FH has recently been assessed for safety¹⁰² (Footnote 5). Seventy-three FH children (10.5 ± 0.5 years old at entry) were studied after 5.7 years on a diet containing < 250 mg cholesterol/day and a P/S ratio of 1.5 to 1.0. The mean age, sex and race specific percentiles for height and weight at entry were indistinguishable from those found after dietary treatment. This long-term cholesterol lowering intervention was safe,

well-tolerated and did not adversely affect normal physical growth, development, maturation, behavioral patterns or school achievement. The present better controlled prospective clinical trial with a well-defined control group and using children with more mild elevations of LDL-C, which are more typical of the average hypercholesterolemia will increase knowledge about dietary safety and efficacy. In designing the dietary modification program it is necessary to assure that all essential nutrients are included at their proper level. Among the nutrients of concern are protein, B-complex vitamins, vitamin C, fat-soluble vitamins, iron, zinc, and calcium. Total calorie consumption is critical at this high-growth age.

1.7.1 Protein, Calories, Trace Minerals, and Safety

Two of the major elements needed for growth are protein and calories. In general, a restricted diet for children should not contain any recommendation for a decrease in protein content. The use of lean meat, fish and poultry provides sufficient protein of animal sources in addition to protein from vegetable sources to supply recommended protein needs. The caloric needs of the very active adolescent person requires attention and it is also important to consider that the nutritional needs of the pre-adolescent may vary more in relation to the biological age than the chronological age. Certain workers in the field are concerned that decreasing the total fat in the diet, while not harmful from the standpoint of saturated fat content, may be harmful for excluding "the company that fat usually keeps, e.g., certain micronutrients such as zinc which has relatively high levels in meat. Finally, hypocaloric diets particularly used for the treatment of childhood and adolescent obesity can produce a temporary reduction in the growth curve of such individuals.⁶² However, not all diets for obese children have indicated adverse effects on growth.⁶³

The requirements for trace dietary elements such as iron, calcium and zinc have been reviewed in the pediatric literature by Dwyer.¹⁰³ Modified diets are not to be deficient in essential minerals or vitamins based on standard calculations using RDAs. Again, however, these requirements can vary from individual-to-individual, by the accelerated pattern of growth, or biological age. Consequently, a more detailed assessment of the nutrient requirements in preadolescents is needed, followed through the accelerated growth period of adolescence. One of the changes in the diet recommended is an increase in complex carbohydrates and a decrease in simple sugars. Such a change may provide an additional source of minerals and vitamins that are not often found in the foods that many adolescent children consume.

1.7.2 P/S Ratio and Safety

There may be an upper limit for an optimal P/S ratio. In adults, the use of diets containing a P/S ratio of 2 or higher have been found to be associated with more cases of gallstones and cancer deaths,¹⁰⁴ and a P/S ratio of 4 lowers significantly HDL-C and apoA-I.¹⁰⁵ Habitual population diets almost never have a P/S ratio greater than 1 and are usually below 0.8. For these reasons the diet should contain no more than 10% of the calories from polyunsaturated fat (P/S ratio \leq 1.0), a proportion of fat that is consumed in countries like Italy, Greece, and Israel. On the contrary, a high total fat intake is associated with carcinomas, particularly breast and colon cancer. The Committee on Diet, Nutrition and Cancer of the National Academy of Sciences has recommended a reduction in total fat to about 30% of calories, and an increase in the consumption of fiber and complex carbohydrates.¹⁰⁶

1.8 Behavioral Change in Dietary Intervention

1.8.1 Obesity Studies

Most research with children involving alterations of eating problems has been concerned with obesity, and most of the controlled studies have examined the effects of behavior modification programs. The results of such studies with adults have suggested that behavioral treatments can reliably reduce weight in adults,¹⁰⁷ but only in small amounts. Treatment is more effective with mild to moderately obese adults than with severely obese adults.¹⁰⁷

Preventing and controlling obesity has certain important parallels to reducing lipid intake for children (Footnote 6). Both conditions are risk factors for coronary heart disease, but for most of the children the severe medical consequences of heart disease will not be experienced until adulthood. In contrast, for children the pleasurable aspects of eating their preferred foods, many of which need to be decreased while on a low cholesterol diet, is immediate.

Clinicians are thus faced with the challenge of teaching self-control -- teaching individuals to relinquish short-term benefits for potentially greater, long-term gains. Using techniques that have been most effective in teaching self-control, especially self-control of eating behavior, is the present logical starting point for altering cholesterol intake in children. In addition, since a significant number of children with high cholesterol are also obese, reducing the intake of fat can contribute to reductions of weight gain (although not necessarily weight loss in growing children).

Several behavioral treatment programs in recent years have shown success in modifying the eating behavior and weight of obese children. One such behavioral treatment program has had success in teaching the children a color-coded diet to which rewards were made contingent, in part, on reducing "red" (high calorie) foods.¹⁰⁸ The diet is based upon a fat modified diet¹⁰⁹ to decrease intake of saturated fat cholesterol and sugar while increasing nutrient density per calorie. Contingency management training, coupled with diet, has been shown to be

significantly more effective than no treatment for reducing percent overweight in 8-12 year old children. Adding an exercise component did not increase effectiveness of weight reduction.¹¹⁰ An average 15% reduction in percent overweight was produced for both a diet plus contingency management and a diet + contingency management + exercise group. Changes in parents total body mass index (BMI) was highly related to BMI changes in children. Similarly, children of parents receiving training in a two-session parent-training course, prior to specific training for weight reduction, showed a slower weight gain (in percent overweight) than did children whose families received only instructions concerning weight loss.¹¹¹

These programs all have certain common elements. Emphasis is placed upon (1) teaching self-monitoring of high fat foods; (2) teaching stimulus control techniques (what and where to eat); (3) instructions about the amounts to eat either by training the child and family to reduce food portions or by reducing overall calories; and (4) rewards for compliance with the program and/or weight loss. Programs have varied on the use of preferred activity vs. monetary rewards for compliance and weight loss. Most programs use some form of deposit that is returned to the family for attendance, or given to the children for weight loss. Also successful programs, including SPIN, include instruction for the parents, and self-control training for the child or adolescent. Better success was reported in a program in which mothers and young adolescents met separately.¹¹² Training the parents in general child management techniques appears to be beneficial.¹¹³

1.8.2 Diabetes Studies

Another area of dietary behavioral modification literature concerns juvenile diabetics. A theoretical model which has recently been applied to school age youngsters and successfully produced changes in dietary practices among diabetic

children is the social learning theory. This is a powerful change method which uses social modeling and guided practice to teach persons how to accomplish personal goals.¹¹⁴ The social learning model of behavior proposes four principal sources of influence on behavior: environmental, personal, physiological and behavioral.¹¹⁵⁻¹¹⁶ Theoretically it is based on the concept that an individual is influenced by his/her environment. The environmental influences are evaluated by the individual in relation to personal competencies, perceptions, values, expectations, beliefs, emotions, and physical states. These variables will determine what actions the person will take, if any. The notion that persons can influence the external environment is central to the social learning model. So that personal influence skills (i.e., behavior competencies and methods of processing environmental information (i.e., thoughts, expectations) will help determine a persons behavior.

Children apparently have difficulty understanding a classification system that places foods into groups largely on the basis of their nutrient classification (i.e., the four food groups).¹¹⁷⁻¹¹⁹

Studies investigating diabetic control have focused on treatment which reduced the impact of environmental stress and reinforces coping capacity. Baker¹²⁰ found psychological therapies more effective than chemical intervention. The success of family therapy and multifamily group therapy in improving control has been demonstrated.¹²¹⁻¹²² Behavioral treatment¹²³⁻¹²⁵ and educational methods¹²⁶⁻¹³¹ for increasing control have also been supported by research findings. Accumulating evidence indicates that the important variables of personality, stress, compliance, and family factors comprise a social mileau which influences control.¹³² In addition, personality constructs such as self-efficiency¹³³ and ego development¹³⁴⁻¹³⁶ correlated significantly with dietary control. Further studies suggest that the acquisition of social coping skills allow the reduction of

environmental stress due to negative social labeling.¹³⁷⁻¹³⁹ A social learning theory model to increase healthy eating patterns in children included environmental, behavioral and personal attributes in a school based treatment program, but did not include psychological, social or physiological measures; family based interventions; nor an at risk population.¹⁴⁰

In the absence of studies of nutritional intervention with children at risk for CHD, findings from studies of diabetic control in children appear to provide relevant and useful guidelines regarding the psychosocial aspects for factors of dietary control including motivation, compliance, adherence, and transfer/generalization.

1.9 Clinical Trials

Clinical trials work by comparing treatment effects between treatment and nonintervention groups.¹⁴¹ The treatment groups in this study will be composed of children with high LDL-C who are suitable for treatment with a dietary intervention program ("special care"). Published opinions on indications for intervention range widely from insistence on dietary regimens to reduce cholesterol in any children above the median cholesterol level to skepticism about the value and safety of treatment in children with asymptomatic hyperlipidemia. In both Finland and the U.S. it has been shown that interventions can reduce cholesterol level in target populations.^{73,75} In the present study it is important to ascertain which children are appropriate for intervention.

The treatment groups to be presently compared are composed not of all children suitable for treatment, but of children suitable for treatment who agree and whose families agree to participate in the trial. Much is known about recruitment strategies to identify suitable children and then recruit them for a randomized clinical trial.¹⁴² One widely known but often forgotten piece of

existing knowledge is that recruitment and obtaining informed consent is highly labor-intensive. The Coordinating Center in this study will have to work with each Clinical Center to help it develop its best recruitment strategy, recruitment sources, and consent procedures. New and successful recruitment strategies are important as there is always room for improvement in recruitment efficiency.

The measurement of treatment compliance and acceptability is an area for innovation in pediatric, dietary clinical trials. Pill count and urine tests have been the mainstays of compliance testing in drug trials. The development of new methods from diet recalls or records to be compared to diet prescription, from dietary intervention session attendance and participation, and even from biochemical measurements is a feature of the present trial. In the Bogalusa Study, an improved twenty-four hour dietary recall for use in children has been developed and validated,¹⁴³ and it is clear that, for the present study, their approach is most successful in assessing group dietary intake with the aim of contrasting the control and experimental groups. The use of this method, or of a similarly based instrument adapted for children is included in this trial. Acceptability measures are under development so that they apply to both study groups and are of even greater value when applied to children outside this study.

It is possible that a minority of healthy, free-living children in the United States consider their diets acceptable. Among the measures to be developed could be the number of meals or days the children like their diets, the proportions of meals completed, and even a scale for level of satisfaction with diet. This study fills gaps in existing knowledge of compliance and acceptability measurement methods. Although not adapted to children there are published questionnaires to measure dietary restraint, disinhibition and hunger in obese adults.¹⁴⁴

TC and LDL-C levels have been measured in multicenter clinical trials¹⁴⁵⁻¹⁴⁶ and standardization of the measurement methods are known to be important for achieving

data of sufficient quality from which to draw conclusions. This clinical trial develops methods for capillary blood sampling and cost-effectiveness of methods for lipoprotein assays.¹⁴⁷

No one has yet identified the most desirable dietary programs.^{67-70, 97-100,135,147} There is experience with a feasibility study to select a "best" treatment in another study, the NHLBI Thrombolysis in Myocardial Infarction Study.¹⁴⁸ One way to identify a best cholesterol lowering diet would be to design the feasibility study for the proposed project as a clinical trial in which two or more diets or dietary intervention approaches are compared.

Methods for assessment of growth, development and nutritional status rest on a strong base of existing knowledge in pediatrics. This study provides a comparison of growth, development and nutritional status between the "special care" group and the "control" group as a measure of dietary program safety.

Diagnostic labeling has long been known to have adverse effects.¹⁴⁹⁻¹⁵⁰ This clinical trial attempts to turn risk factor identification from an ill health label with negative connotation into a seed for the development of self-confidence and dietary control with positive connotation.

1.10 Footnotes

1.10.1 Footnote 1

About one-third of children were selected because their parents had premature CHD, hypercholesterolemia or hypertriglyceridemia.¹⁵¹⁻¹⁵³ Schrott and co-workers¹⁵⁴ found a significantly higher coronary mortality in the adult relatives of school children with plasma cholesterol levels in the middle group or the lower group (<5th percentile). In the LRC Family Study, Morrison et al.¹⁵⁵ reported that the frequencies of top decile plasma TC and LDL-C levels in offspring and siblings of hypercholesterolemic probands from the general population, were increased

twofold to threefold to fivefold, respectively, compared with such first degree relatives of normal probands. In summary, available evidence indicates that the quantification of risk factors for CHD in children predicts risk factors in their parents and vice-versa.

1.10.2 Footnote 2

FH is an autosomal dominant that has a gene dosage effect.³⁹ FH is completely expressed at birth and early in childhood¹⁵⁶⁻¹⁵⁷ and is the most commonly recognized disorder of lipoprotein metabolism in childhood, affecting 1,200 to 1,500 children.³⁹ FH heterozygotes have plasma levels of total and LDL cholesterol that are elevated about twofold to threefold above normal, while FH homozygotes have levels that are about fivefold to sixfold elevated.¹⁵⁷⁻¹⁵⁸ The heterozygous FH child is clinically asymptomatic in the first decade; 10-15% of heterozygotes developed tendon xanthomas during the second decade, and occasionally, a FH heterozygote will develop angina pectoris in the late teenage years.¹⁵⁷ Homozygous FH children develop plantar xanthomas usually by five years of age, and tendon and tuberous xanthomas develop between the ages of five and fifteen years.¹⁵⁸ Angina pectoris and myocardial infarction and aortic stenosis usually occur in the second decade but have often been found as early as six years of age.^{39, 158} Goldstein, Brown and coworkers³⁹ discovered that cells from FH homozygotes lack functional LDL receptors while FH heterozygous cells have about half the normal number of LDL receptors.

1.10.3 Footnote 3

At least 25% of the children seen in Kwiterovich's lipid clinic who have mild hypercholesterolemia (between the 90th and 99th percentile) have hyperapoB.

1.10.4 Footnote 4

A number of groups in recent years have carried out intervention studies utilizing dietary counseling in individuals in order to demonstrate the feasibility and safety of this type of intervention in both normal children and those with FH. The results of these studies, carried out in both normal and hyperlipidemic children, and have recently been reviewed.¹⁵⁹ In boarding schools, reductions in dietary fat, increases in dietary P/S ratios¹⁶⁰⁻¹⁶¹ and those reducing dietary cholesterol¹⁶² resulted in reduction of plasma cholesterol. Those with a higher entry level cholesterol had a large percent fall. In free-living youngsters aged 12-18 years old, a diet high in polyunsaturated fat (20-25% of calories) with a P/S ratio of 2.5:1 to 2.0:1 resulted in a mean serum cholesterol reduction of 20-25%. Glueck¹⁶³ was able to effect a decrease in total cholesterol and a decrease in LDL-C in 11 free-living normal siblings, aged 6-17 years in a three month period by reducing the total fat from 41% of calories to 33% and by increasing the P/S ratio from 0.65 at baseline to 1.73, even with an increase in dietary cholesterol of 100 mg per day, to 450 mg. This effect was further reduced, but not significantly so in the next three-month period when the dietary cholesterol was reduced to 160. Plasma TC and LDL-C increased significantly over the next three month period with a diet of 450 mg cholesterol, 40% fat and a P/S ratio of 0.4.

Children who are heterozygous for FH respond to dietary manipulations, but often not enough to normalize lipid values,¹⁶³⁻¹⁶⁴ This was confirmed by the study cited above¹⁶³ in the FH siblings in whom LDL-C never fell below the 95th percentile. The FH children seemed more responsive to dietary cholesterol than their normal siblings. Kwiterovich,¹⁶⁵ also working with FH children, used NIH type II diets containing 300 mg of cholesterol per day with a P/S ratio of two for most (with the exception of the type II_b children with an LDL-C of > 170, who were given a P/S of one). Simple sugar was also restricted for those with II_b.

Follow-up period ranged up to 39 weeks. This study confirmed others that a free-living population of type II children could achieve a fall of 10-15%, but added the observation that LDL apoB and LDL-C is cited. The safety of using these diets long-term in growing children has been questioned. Glueck et al. recently completed a five to eight year study¹⁶⁶ with FH children using either diet alone (250 mg/chol/day, a P/S ratio of 1-1.5 and > 35% of calories of fat) or a combination of diet plus a bile acid binding resin in which a smaller percent of weight measurements were greater than baseline percentile than normal children on an ad libitum diet. He felt this might reflect the reduction in fat intake and further concluded normal growth and development were not affected. The diet alone reduced mean plasma TC by 9.6% with a 29% achieving a reduction of > 14% and 29% reduction of > 21%.

Thus a series of studies, most short term, have examined the effect of dietary treatment of hypercholesterolemia. In the majority, but not all of these, the dietary cholesterol was reduced from < 300 down to 160 mg/day, total fat was reduced to < 35% and P/S ratios increased to 1.5 to 2. Blood total cholesterol reductions ranged from 20-25% in an extreme study where normal subjects consumed 20-25% of their calories as polyunsaturated fat to the more commonly reported 10-15% reduction. The diet proposed is analogous to AHA phase two diet, and would appear to be capable of achieving a reduction in total plasma cholesterol from the upper decile to below the 75th percentile of distribution without major untoward effects. It would also appear to be relatively easily attainable.

1.10.5 Footnote 5

Humans are capable of endogenous synthesis of cholesterol and saturated fats. The only essential fatty acid are polyunsaturated. There is no theoretical reason why a decrease in cholesterol and saturated fat in the diet per se may be

deleterious to growth and development provided there is a sufficient supply of calories, protein, vitamins, minerals, and other nutrients. The use of commercial formulas in this country for decades has provided some practical experience in this regard. Fomon and co-workers¹⁶⁷ examined 469 at age eight years who had been studied intensively in a metabolic unit from 8 to 112 days of age. There were no differences in height or weight between the infants who were breast fed and those who were formula fed. Friedman and Goldberg¹⁶⁸ found no significant difference between the percentiles for height, weight or head circumference at three years of age in a group on a diet low in cholesterol and saturated fat with a P/S ratio of one from birth.

1.10.6 Footnote 6

There have been two generations of studies of weight reduction in children.¹¹² The first generation involved application of principles drawn from studies of adults and were not successful, showing considerable variability among subject and little evidence for positive long-term results. These early studies with children and adolescents tended to be rather poorly controlled.¹⁰⁸ The next generation of studies, however, has been more promising, with studies emphasizing family involvement, exercise, nutrition, and traditional behavioral techniques. These more recent studies have been both better controlled and more optimistic about the possibility of effectively reducing weight gain in children.

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CHAPTER 2

OVERVIEW OF THE MAJOR DESIGN FEATURES

2.1 Study Objectives

The primary objectives of The Dietary Intervention Study in Children (DISC I and DISC II) are to assess feasibility, acceptability, efficacy, and safety of dietary intervention in children age 8-10 at baseline with elevated low density lipoprotein cholesterol (LDL-C) levels. Assessment of feasibility and acceptability will be the primary focus of the feasibility study, while assessment of efficacy and safety will be the primary focus of the DISC I and II full-scale trial. The primary outcome variable for efficacy in DISC I is 36-month minus baseline difference in LDL-C.

2.2 Study Phases

DISC I is divided into four phases:

Phase IA (12/86 - 7/87): Planning and Protocol development. Phase IB (8/87 - 11/88): Feasibility study.

Phase II (12/88 - 8/93): Full-scale trial.

Phase III (9/93 - 11/94): Data analysis.

The feasibility study will consist of a 5-month participant recruitment period and a 12-month intervention and follow-up period. On the basis of data from the baseline and 6-month follow-up visits, the DISC Data and Safety Monitoring Committee will determine the feasibility of the full-scale trial, and decide whether to proceed with the full-scale trial. The feasibility study is designed so that if the full-scale trial is approved, feasibility study

participants can be included as part of the full-scale trial and followed until the end of the full-scale trial.

The DISC I full-scale trial will have an 30-month participant recruitment period and a 64-month follow-up period, with participants enrolled early in the recruitment period followed for 48 months and those enrolled at the end of the period followed for 36 months.

The annual follow-up visits in DISC II will start in August, 1993 and continue through January, 2001. Each participant will be followed until their eighteenth birthday, i.e., their final visit. Because of the variable age at randomization into DISC I (ages 8-9 for girls and ages 9-10 for boys), this common termination age will result in some participants being seen for their final visit (FV01) as early as 1996.

Extraordinary efforts will be undertaken to see all participants at their DISC II final visit. In addition to making every effort to see the participants at the clinical center itself, the DISC clinics are prepared to conduct home visits (using a standard off-site visit protocol), fly participants to the clinical center, fly clinic staff to the participants, or make arrangements with local medical personnel to collect the essential data for endpoint analysis in DISC II (i.e., height, weight, lipids). Additional incentives will be offered to the participants for completing the final visit.

2.3 Size and Nature of Participant Group and Eligibility Criteria

DISC I will enroll approximately 120 children in the feasibility study and 480 additional children in the full-scale trial. Boys 9-10 years old and girls 8-9 years old with mean of two LDL-C levels within the 80th to 98th percentile range of the Lipid Research Clinic values for children of the same age will be enrolled. Exclusion criteria include obesity (weight for height greater than 90th

percentile), medical conditions or use of medications that affect growth and/or lipids, current adherence to a lipid-lowering diet or factors likely to produce diet modification in the control group, and problems likely to reduce adherence to the intervention. A complete list of eligibility criteria is presented in Chapter 4.

Prospective participants will be identified via mass screening for elevated serum total cholesterol levels in five of the clinical centers, and referrals from pediatricians and pediatric clinics in one clinical center.

2.4 Intervention

Participants will be randomly assigned to either an intervention or a usual care (control) group. Randomization will be stratified by clinical center, age, and gender. Because of the nature of the intervention, treatment assignment will not be blinded to either the participant nor the interventionists. Interventionists will remain unblinded to individual lipid results after the 36-month visit, but will remain blinded to group lipid data. In addition, the data collection staff will be blinded to the participant's treatment group.

The intervention is designed to involve both the children and their parents.

Intervention group participants will be enrolled in weekly group and individual intervention sessions where they and their parents will receive instruction and assistance with behavior changes needed to modify their diets to produce lowered serum LDL-C levels. After 15 initial group and individual intervention sessions, families will be asked to attend monthly maintenance sessions. DISC I dietary goals of intervention are: no more than 28% of total calories from fat, no more than 8% of total calories from saturated fatty acids, at least 9% of total calories from polyunsaturated fatty acids, and no more than 75 mg of dietary cholesterol per 1000 kcal, not to exceed 150 mg/day. For DISC II the same

intervention goals were adopted with the exception of the goal for dietary cholesterol where the 150 mg/day limitation was dropped to accommodate the higher caloric intakes of older children and adolescents.

Participants assigned to the control group will be prescribed "usual care," that is, informed of their elevated serum cholesterol level and given an information packet at the first screening visit. Subsequent contacts with the control group participants will be limited to annual follow-up visits.

2.5 Visit Schedule and Types of Information Collected

Eligibility of prospective participants will be determined during a series of three screening visits and a baseline visit. Prior to the first Screening Visit (SV01) is a Prescreening Assessment for elevated plasma total cholesterol using a desk-top cholesterol analyzer on a capillary blood sample or analyzing a venous blood sample at a local laboratory. Venous blood samples will be taken at Screening Visits 1 and 2 (SV1 and SV2) and sent to a Central Lipoprotein Laboratory for determination of serum total cholesterol, HDL-cholesterol, and triglycerides, and hence, by calculation, LDL-C. Assessment of other eligibility and exclusion criteria will also be made at SV1 and SV2. Eligible volunteers will be asked to attend the Baseline Visit (BV) at which final baseline measurements will be made. Following this the treatment group will be randomly assigned by the Coordinating Center. Participants assigned to the intervention group will attend both group and individual intervention sessions. All participants, both treatment and control, will come to the clinic at annual follow-up visits for collection of biochemical, clinical, anthropometric, nutrition, physical activity, and psychosocial data. Venipuncture will be required in DISC I at the first and second screening visits, 6 months (feasibility study only), 12 and 36 months; and in DISC II at the Year 5, Year 7, Year 9 and final follow-up visits.

2.6 Participating Units

Institutions participating in DISC are: the National Heart, Lung, and Blood Institute Program Office; a Coordinating Center at Maryland Medical Research Institute in Baltimore; six Clinical Centers located at Johns Hopkins University in Baltimore, Northwestern University in Chicago, University of Iowa in Iowa City, New Jersey Medical School in Newark, Louisiana State University/Children's Hospital in New Orleans, and Kaiser Permanente Center for Health Research in Portland, Oregon; a CDC-standardized central Lipoprotein Laboratory at Johns Hopkins Hospital in Baltimore, Central Laboratories for non-lipid determinations at Johns Hopkins Hospital in Baltimore and the Centers for Disease Control in Atlanta, and a Nutrition Coding Center at the University of Minnesota in Minneapolis. The study is governed by a Steering Committee made up of investigators from each Clinical Center, the Coordinating Center, and the Program Office, with oversight by a Data and Safety Monitoring Committee made up of scientists not directly associated with DISC.

CHAPTER 3

OBJECTIVES AND DESIGN OF THE TRIAL

3.1 Study Objectives and Research Questions

The primary objectives of the Dietary Intervention Study in Children (DISC and DISC II) are to assess the feasibility, acceptability, efficacy, and safety of dietary intervention in children age 8-10 with primary elevated low density lipoprotein cholesterol (LDL-C) levels. Assessment of feasibility and acceptability will be the primary focus of the feasibility study, while assessment of efficacy and safety will be the primary focus of the full-scale study.

The study will investigate the following research questions:

1. Can dietary intervention reduce LDL-C levels in hyperlipidemic children, and can such a reduction be maintained over a 36-month follow-up period?
2. Is a diet lower in fat and cholesterol than the usual American diet acceptable to children of this age and their families?
3. Does adherence to the DISC dietary regimen maintain optimal nutrition status for growing children?
4. What baseline characteristics of children and their families predict compliance with the DISC dietary regimen?
5. What is the effect of intervention on the cholesterol levels of family members?
6. What are the patterns of changes over time in lipoproteins and apoproteins in children in the control and intervention groups?
7. Is the dietary intervention safe in terms of growth rate, biological maturation, and psychosocial status?

8. Do children in the intervention group experience behavior changes (positive or negative) as a result of being identified as different from their peer group?
9. What are the psychological responses (positive or negative) to the diagnostic labeling and dietary instructions?

3.2 Study Phases and Timetable

DISC I is divided into four phases:

Phase IA (12/86 - 7/87): Planning and Protocol development.

Phase IB (8/87 - 11/88): Feasibility study.

Phase II (12/88 - 8/93): Full-scale trial.

Phase III (9/93 - 11/94): Data analysis.

The feasibility study will consist of a 5-month participant recruitment period and a 12-month intervention and follow-up period, with the following anticipated timetable:

August 1, 1987 - October 31, 1987: Prescreening Assessment.

October 1, 1987 - November 30, 1987: Screening Visit 1.

November 1, 1987 - December 31, 1987: Screening Visit 2.

December 1, 1987 - January 15, 1988: Baseline Visit.

January 1, 1988 - January 31, 1988: Randomization and first intervention visit.

June 1, 1988 - July 15, 1988: 6-month data collection visit.

December 1, 1988 - January 15, 1989: 12-month data collection visit. The time periods given above for the 6 and 12 months visits reflect the anniversary dates based on the randomization visit. A time window of two months before and after the anniversary date (see Section 9.2 for details) will be acceptable for completing the follow-up data collection visits in both the feasibility study and

the full-scale trial. On the basis of data from the baseline and 6-month follow-up visits, the DISC Data and Safety Monitoring Committee will determine the feasibility of the full-scale trial, and decide whether to proceed with the full-scale trial. If the full-scale trial is not considered feasible on the basis of 6-month data, a decision will be made at that time whether to continue the feasibility study through the 12-month follow-up visit. The feasibility study is designed so that if the full-scale trial is approved, feasibility study participants can be included as part of the full-scale trial and followed until the end of the full-scale trial, provided that no major changes are made in the Protocol for the full-scale trial.

The DISC I full-scale trial will have an 30-month participant screening and recruitment period and a 64-month follow-up period, with participants enrolled early in the recruitment period followed for 48 months and those enrolled at the end of the period followed for 36 months. The following timetable is anticipated for the DISC I full-scale trial:

October 1, 1988 - May 31, 1989: Prescreening Assessment.

December 1, 1988 - June 30, 1989: Screening Visit 1.

January 1, 1989 - July 30, 1989: Screening Visit 2.

February 1, 1989 - August 31, 1989: Baseline Visit.

February 15, 1989 - September 15, 1989: Randomization and first
intervention visit.

August 1, 1989 - February 28, 1990: 6-month data collection visit.

February 1, 1990 - August 31, 1990: 12-month data collection visit.

February 1, 1991 - August 31, 1991: 24-month data collection visit.

February 1, 1992 - August 31, 1992: 36-month data collection visit.

February 1, 1993 - August 31, 1993: 48-month data collection visit
(for 4/7 of the participants).

The DISC II extension of the full-scale trial will continue the DISC I sequence of visits on the following annual schedule:
August, 1993 - January, 1995: 48-month visits (3/7 of participants).

February, 1994 - January, 1996: 60-month visits (Year 5).

February, 1994 - January, 1997: 72-month visits (Year 6).

February, 1995 - January, 1998: 84-month visits (Year 7).

February, 1996 - January, 1999: 96-month visits (Year 8).

February, 1997 - January, 2000: 108-month visits (Year 9).

February, 1996 - January, 2001: Final visits.

3.3 Overall Design

Boys age 9-10 and girls age 8-9 with elevated serum LDL-C levels will be randomly assigned to either a dietary intervention or a control group. The different age ranges for boys and girls are due to the fact that girls enter into puberty on the average about one year earlier than boys. The randomization will be balanced between the two treatment groups within age, gender, and clinical center strata (see Chapter 6). The children in the intervention group, along with their parents, will be asked to come to the clinic for individual and group intervention sessions where they will receive instruction and assistance with behavior changes needed to modify their diets to produce lowered serum LDL-C levels. Children in the control group will be prescribed "usual care," that is, informed of their elevated serum LDL-C levels and given an information packet during the first screening visit. Subsequent contacts with the control group participants will be limited to annual data collection visits.

The safety and efficacy of the dietary intervention will be assessed in both the intervention and the control groups by collection of biochemical, anthropometric, clinical, nutritional, and psychosocial data at baseline, and 12,

36, 60, 84 month and final visits, and collection of only anthropometric data at 6, 24, 48, 72, 96, and 108 months. Anthropometric, clinical, nutrition and lipid data will be collected in a single-blind fashion, i.e., with the data collectors not aware of the participants' treatment group assignment. Adherence to and acceptance of the dietary intervention will be assessed in the intervention group.

3.4 Outcome Measures

3.4.1 Feasibility and Acceptability

The primary outcomes of concern in the feasibility study are the ability of clinics to recruit individuals for this study and the ability of the children to adhere to a fat-modified or lipid-lowering diet while maintaining nutritional adequacy. Change in LDL-C will also be measured in the feasibility study but is not expected to give conclusive results because of the small number of participants. Various feasibility and acceptability outcomes are discussed in the following sections.

3.4.1.1 Ability to Achieve Recruitment Goal

A crucial outcome of the feasibility study is the ability of the six clinical centers to achieve the recruitment goal of 20 participants/clinic during a five-month recruitment period. Failure to achieve an enrollment of 20/clinic in five months of recruitment will cast doubt on the ability to recruit 80/clinic during an 18-month recruitment period in the full-scale trial.

Yields from different approaches to screening and recruitment of study participants by the different clinics will be evaluated during the feasibility study and adjustments made, if necessary, for the full-scale trial.

3.4.1.2 Ability to Adhere to Diet

The ability of the intervention group children to maintain a fat-modified or

lipid-lowering diet during the feasibility period of intervention will be assessed primarily by means of dietary intake data obtained on the children at baseline, and six months and at selected intervention sessions. These data obtained during the first six months of intervention will be crucial with regard to deciding whether to proceed to the full-scale trial.

3.4.1.3 Ability to Maintain Nutritional Adequacy

This will be assessed by evaluating changes (or lack thereof) from baseline in intake of vitamins, minerals, and other nutrients based on the dietary intake data obtained on the children at baseline, and six months and at selected intervention sessions.

3.4.1.4 Acceptability of the Diet

A good serum LDL-C response and good adherence to the diet, as assessed by dietary intake data, would suggest that the diet is acceptable. However, it is possible that some participants will adhere to the diet for a few months for the benefit of science, even though they prefer other food. Thus, questions will be asked at certain intervention sessions to try to ascertain the parents' and the children's attitudes toward the diet.

3.4.1.5 Attendance at the Intervention Sessions and Data Collection Visits

Another aspect of feasibility relates to the faithfulness of completing the requisite follow-up visits (so that the necessary data can be collected) and attending the intervention sessions (so that the requisite dietary information, advice, and counselling can be received). Poor attendance at the intervention sessions is likely to be a marker for poor adherence to the diet and poor acceptability of the diet.

3.4.1.6 Maintenance of an Intervention-Free Control Group

The 6-month serum LDL-C data will be compared with baseline levels in control group participants to determine whether the control group participants are showing major changes in serum LDL-C that might make it impossible to detect an effect due to the intervention.

3.4.1.7 Change in LDL-Cholesterol

Because of the small number of participants in the feasibility study, it is not expected that a significant difference between the intervention and control groups will be detected with respect to change in LDL-C from baseline. However, if no decrease in LDL-C from baseline to 6 months is observed in the intervention group, or if less of a decrease is observed in the intervention group than in the control group, serious consideration must be given to whether it will be worthwhile proceeding to the full-scale trial. If this were to occur, a decision to proceed to the full-scale trial will be postponed until the 12-month data are available from the feasibility study.

3.4.2 Efficacy

The primary outcome for efficacy of the intervention in the DISC I full-scale trial is the difference in the 36-month minus baseline serum LDL-C levels between the intervention and control groups. Both the 36-month and the baseline LDL-C levels will be based on the mean of the two LDL-C determinations made approximately a month apart.

The reason for using the change in LDL-C from baseline is to reduce (though not eliminate) the problem of possible differences between the intervention and control groups with respect to distribution of LDL-C at baseline.

The reason for using the 36-month value rather than the mean of the 12 and 36-month values is that one of the primary objectives of DISC is to assess the long-term (i.e., multi-year) efficacy of dietary intervention. It is possible that the difference between intervention and control groups in lowering of LDL-C from baseline will be greater at 12 months than 36 months because of reduced compliance to the dietary regimen in the intervention group and possibly increased attention to fat-modified or lipid-lowering diets by families in the control group

with the passage of time.

The evaluation of efficacy may become particularly complicated if the dietary intervention has the effect of delaying sexual maturation, since LDL-C tends to decrease by several mg/dl during puberty, and since three years of follow-up will leave many of the participants in the middle of the pubertal period. For this reason, there is benefit in collecting data on LDL-C, growth parameters, and sexual maturation at 48 months for those enrolled early in the recruitment period.

Secondary outcomes for efficacy in DISC I include change from baseline to 12 months in LDL-C and changes from baseline to 12 and 36 months in total cholesterol (TC). LDL-C and TC values at other time points as well as clinical and psychosocial measures obtained at the various time points will also be evaluated for evidence of efficacy of the intervention.

3.4.3 Safety

The primary outcome for safety for the DISC I full-scale trial will be height attained at the 36 month follow-up visit because earlier follow-up will not have a chance to produce large enough levels of retardation in height. The primary outcome for safety in the extended DISC II follow-up trial will be final adult height attained at age 18. A diet that reduces the final adult height attained in the intervention group, compared to the control group, will not be considered safe for the purposes of this trial. If the diet reduces height attained after 36 months of follow-up in the intervention group, compared to the control group, the diet may be unsafe. One possible test for this is to compare the mean height at 36 months between the two treatment groups using a linear model with height at 36 months as the dependent variable and baseline height and treatment group as the independent variables. This model produces an estimate of

the effect of treatment on attained height at 36 months adjusting for baseline height. Because of the differential growth patterns in boys and girls, this model will be run separately for the two genders.

If the DISC diet reduces height attained at 36 months follow-up in the intervention group, compared to the control group, and the statistical significance of this reduction can be attributed to a retardation of sexual maturity, then the safety of the diet cannot be determined until final adult height is attained. Height at full sexual maturity can be taken as a surrogate for final adult height with only a small loss of precision. The test for difference in height at 36 months, taking into account maturation stage, will be similar to the one described above with the addition of a term for Tanner staging.

The initial test performed will involve the model including terms for treatment group and baseline height as above. If the term for treatment group is significantly different from zero, the model including Tanner stage will be run. For the analysis of height reached at 'full' sexual maturation, the Tanner stage term in the model may not be necessary if all participants have really achieved 'full' sexual maturity. The interpretation of 'full' sexual maturity may not be Tanner stage 5 in all cases. Further, there may be a few participants who have not reached 'full' sexual maturity by the end of the study, due to intense athletic training (or other reasons). For these reasons, it will be safest to include the Tanner stage term in this model unless all participants have reached Tanner stage 5. If the DISC diet reduces height attained at 36 months in the intervention group, compared to the control group, and the statistical significance of this reduction cannot be explained by a retardation of sexual maturity, then the diet will be considered potentially unsafe. However, if the reason the statistical significance cannot be explained by a retardation of sexual maturity is excessive variability in the assessment of sexual maturity, the diet

may be safe.

Another primary outcome for the safety of the DISC diet will be serum ferritin level, a measurement of iron stores and an indicator of the nutritional adequacy.

A delay in sexual maturation will be tested as a secondary safety outcome, using methods for ordered categorical data analysis. One possible statistical test is to take a weighted linear combination of the estimated probabilities of being in each of the maturation stages. If the weight 'i' is assigned to maturation stage i, then this test is equivalent to a t-test of maturation stage.

Other secondary outcomes for safety include serum levels of zinc, folate, retinol and albumin as well as the LDL-C/HDL-C ratio. In addition, measures of cognitive development (Woodcock-Johnson Math and Reading Clusters) and child behavior (Achenbach Child Behavior Checklist) will also be tested as secondary outcomes.

3.5 Required Sample Size

The anticipated sample size in DISC is $n = 240$ per treatment group or $2n = 480$ for the full-scale trial. If the feasibility study participants ($n = 60$, $2n = 120$) are included in the full-scale trial, the sample size will be $n = 300$ per group or $2n = 600$. In this section we will consider the size of the intervention effect with respect to LDL-C that can be expected with the anticipated DISC sample sizes, and what the required sample sizes would be for various alternative assumptions.

The primary outcome variable for efficacy in DISC is 36-month minus baseline LDL-C. The following population values for LDL-C have been observed in 8-10 year old children falling within the 75th to 95th percentiles of the distribution of LDL-C in the Bogalusa Study:

Baseline: mean 119.8 mg/dl, standard deviation = 8.35 mg/dl.

36 months: mean = 105.3 mg/dl, standard deviation = 19.59 mg/dl. Baseline, 36 months correlation = 0.225.

Thus, the standard deviation on 36-month minus baseline LDL-C =

$$[8.35^2 + 19.59^2 - 2(.225)(8.35)(19.59)]^{1/2} = 19.49.$$

Note that it can be shown that this standard deviation of 36-month minus baseline LDL-C is virtually the same for participants falling in the 85th to 95th percentiles or the 90th to 98th percentiles of the distribution of LDL-C. The reason for this is that while the standard deviation of the baseline LDL-C is smaller for the smaller percentile ranges, the baseline, 36 months correlations are correspondingly smaller. The standard deviations have not yet been specifically determined from the Bogalusa data for children falling between the 80th and 98th percentiles of LDL-C, the range to be used in DISC. However, following the arguments given above, it seems likely that the standard deviation value of 19.49 will be very close to the correct value.

It should be noted also that LDL-C values found in the Cincinnati Lipid Research Clinics Children's Study for 8-10 year old children have a somewhat higher mean and, curiously, a somewhat lower standard deviation than those from the Bogalusa Study. Thus, the calculations based on the Bogalusa values may be somewhat conservative if the DISC population turns out to be more like the Cincinnati LRC population than that of Bogalusa.

If $\alpha = 0.05$ (two-sided) and power = 0.90, and assuming a standard deviation for 36-month minus baseline LDL-C of 19.49, the sample size for each group is given by

$$n = (1.96 + 1.282)^2(2)(19.49)^2(d_1-d_2)^{-2} \quad ,$$

where d_i denotes the true 36-month minus baseline differences in LDL-C for the intervention group ($i=1$) and the control group ($i=2$). If the total sample size is $2n = 480$ or $n = 240$ per group, the true difference between the two groups

in change in LDL-C from baseline to 36 months must be at least $d_1 - d_2 = 5.77$ mg/dl.

If the feasibility study participants are added in, with $2n = 600$ or $n = 300$ per group, the true difference must be at least 5.16 mg/dl.

Next we consider the difference, $d_1 - d_2$, that might be expected from the diet regimen proposed for DISC. Let SC denote serum cholesterol in mg/dl, let S and P denote percentages of total calories provided by SFA and PUFA, respectively, let C denote dietary cholesterol in mg/1000 kcal, and let the Δ operator denote change in SC, S, P, and/or C from one diet to another.

Keys et al¹ give the following formula for expected change in SC given a particular dietary change involving S, P, and C:

$$\Delta SC = 1.35(2\Delta S - \Delta P) + 1.5 \Delta(C^{1/2}).$$

These authors also give a formula for the mean SC for the men whose data were used to develop this equation:

$$SC = 164 + 1.35(2S - P) + 1.5C^{1/2}.$$

Note that these equations were based on data from adult males who are physically healthy schizophrenics in Hastings (MN) State Hospital and mentally defectives in Faribault (MN) State School and Hospital.

Now we must assume (for want of a better approach) that the equation $SC = 164 + 1.35(2S - P) + 1.5C^{1/2}$ applies to children. For the assumed baseline diet of the DISC children (i.e., 14% SFA, 5.5% PUFA, and 138 mg/1000 kcal dietary cholesterol), $SC = 212$ mg/dl. For the anticipated change from baseline diet to DISC diet (i.e., $\Delta S = -6$, $\Delta P = +3.5$, and $\Delta(C^{1/2}) = -3.09$), $\Delta SC = 25.5$. The anticipated decrease in SC of 25.5 mg/dl applies to a child with a baseline SC of 212 mg/dl. Keys et al. give a further formula that adjusts SC for baseline levels of SC differing from the "standard" of 212 mg/dl:

$$\overline{\epsilon SC} = \overline{\epsilon SC}[-.84 + 1.84\overline{SC}/\overline{SC}],$$

where $\overline{SC} = 212$ mg/dl and $\overline{\epsilon SC} = 25.5$ mg/dl.

Now let us consider the anticipated distribution of SC in DISC children. Data from the Cincinnati LRC center,² adjusted to an anticipated distribution in DISC of 45% white males, 45% white females, 5% black males, and 5% black females, give a mean SC of 161 with a standard deviation of 21. Assuming that SC is normally distributed (not exactly true but close enough for our purposes), we obtain values of 175.2, 178.7, 182.8, 187.9, 195.5, and 204.1 for the 75th, 80th, 85th, 90th, 95th, and 98th percentiles of the SC distribution, respectively. From these values we compute the following mean SC's for various intervals of the SC distribution, and the corresponding ϵ SC's compared from the Keys formula,

$$\overline{\epsilon SC} = 25.5[-.84 + 1.84\overline{SC}/212]:$$

<u>Percentile Range</u>	<u>Mean SC</u>	<u>ϵSC</u>	<u>% ϵSC</u>
95 - 98	199.8	22.8	11.4
90 - 95	191.7	21.0	11.0
85 - 90	185.3	19.6	10.6
80 - 85	180.7	18.6	10.3
75 - 80	176.9	17.7	10.0
85 - 98	191.1	20.9	10.9
80 - 98	188.2	20.2	10.8
75 - 98	185.8	19.7	10.6

In the calculations that follow, we will assume a ϵ SC of 19.7 mg/dl corresponding to a 75-98 percentile range at baseline since an 80-98 percentile range of observed SC levels corresponds approximately to a 75-98 percentile range of true SC levels (because of regression to the mean).

The results derived above are for serum total cholesterol TC. Let us

extrapolate these findings to LDL-C by assuming that the entire decrease in TC is confined to the LDL fraction. The results from LRC suggest that this may be a reasonable assumption, for adults at least; in that study the absolute decrease in LDL-C was actually greater than the decrease in TC.³

Next, we assume a dietary-induced decrease of 4.5% (or 5.4 mg/dl) in the control group. Thus, assuming a reduction of 19.7 mg/dl in the intervention group (with full adherence) and a reduction of 5.4 mg/dl in the control group, or $d_1 - d_2 = 19.7 - 5.4 = 14.3$ mg/dl, the required sample size is $n = 40$ per group ($\alpha = 0.05$, power = 0.90).

Let us finally consider what the actual d_1 , and hence the required sample size, might be for different levels of less than perfect adherence. First, define:

Group A: Children at dietary goal at Month 36, i.e., $d_1 = 19.7$.

Group B: Children at 50% of dietary goal at Month 36, i.e., $d_1 = 9.85$.

Group C: Children back to baseline diet at Month 36, i.e., $d_1 = 0$. Next, we compute the required sample size for five different cases based on varying levels of adherence:

Case 1: 100% Group A, 0% Group B, 0% Group C.

$d_1 = 19.7$, $d_1 - d_2 = 14.3$, $n = 40$ per group ($\alpha = 0.05$, power = 0.90).

Case 2: 80% Group A, 10% Group B, 10% Group C.

$d_1 = 16.745$, $d_1 - d_2 = 11.345$, $n = 63$ per group.

Case 3: 60% Group A, 20% Group B, 20% Group C.

$d_1 = 13.79$, $d_1 - d_2 = 8.39$, $n = 114$ per group.

Case 4: 50% Group A, 25% Group B, 25% Group C.

$d_1 = 12.3125$, $d_1 - d_2 = 6.9125$, $n = 168$ per group.

Case 5: 40% Group A, 30% Group B, 30% Group C.

$$d_1 = 10.835, d_1 - d_2 = 5.435, n = 271 \text{ per group.}$$

It is assumed that Case 5 is the most likely situation to be observed in DISC. Thus, by combining the feasibility study with the full-scale trial, with a total sample size of 600, there will be 90% power to detect the anticipated difference in LDL-C change from baseline to 36 months.

3.6 References

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CHAPTER 4
PARTICIPANT ELIGIBILITY

4.1 Eligibility Criteria for DISC I

4.1.1 Introduction

Eligibility criteria for the full-scale trial of the Dietary Intervention Study in Children (DISC) are given in this chapter. When changes were made from the feasibility study (FS), the FS eligibility criteria are given in parentheses.

4.1.2 Inclusion Criteria

A child will be eligible for inclusion in DISC if that child meets the following criteria:

- 1.The child is a male between the ages of 8 years 7 months (8 years 10 months in FS) and 10 years 10 months, or a female between the ages of 7 years 10 months and 10 years 1 month (9 years 10 months in FS), as of the day of Screening Visit 1 (SV1) with a window of two weeks on either side of the day of SV1 for satisfying the age eligibility criteria.
- 2.The LDL-cholesterol (LDL-C) value of the fasting venous blood sample at SV1 must be between the 70th and 99th percentile (based on age-sex specific distributions of LDL-C from the Lipid Research Clinics--LRC--Program), as determined by the Central Lipoprotein Laboratory. The average of the fasting venous blood samples from SV1 and Screening Visit 2 (SV2) must be greater than or equal to the 80th percentile and less than or equal to the 98th percentile of the reference distribution.
- 3.The child does not meet any of the exclusion criteria for the study, as listed in Section 4.1.3.

4.1.3 Exclusion Criteria

A child will be excluded from the study if any of the following exclusion criteria apply:

1. Medical conditions which affect growth and/or cholesterol level (if present, the child should be referred for evaluation):

- a. Hypothyroidism (identified by questionnaire at SV1 and serum T4 at SV2).
- b. Nephrotic syndrome (identified by questionnaire at SV1 and serum albumin at SV2).
- c. Dyslipoproteinemia (identified by serum lipoproteins at SV1 and SV2).
- d. History of or active obstructive liver disease (identified by questionnaire at SV1).
- e. Diabetes mellitus (identified by questionnaire at SV1 and serum glucose at SV2).
- f. History of inflammatory bowel disease, such as Crohn's disease (identified by questionnaire at SV1).
- g. History of renal failure (identified by questionnaire at SV1).
- h. Height less than 5th percentile (identified by tables based on data from the Bogalusa Study at SV1 or optionally at the Prescreening Assessment).
- i. Weight for height less than the 5th percentile or greater than the 90th percentile (identified by specially prepared tables based on data from the Bogalusa Study at SV1 or optionally at the Prescreening Assessment).
- j. Systolic blood pressure 125 mm Hg or greater or 4th phase diastolic blood pressure 80 mm Hg or greater at both SV2 and the Baseline Visit (BV).

2. Current use of medications which may affect lipids:

- a. Thiazide diuretics.
- b. Retinoids.
- c. Steroids.
- d. Lipid-lowering medications.
- e. Current use of ritalin, phenobarbital or dilantin (identified by questionnaire at SV1).

3. Factors likely to increase adherence to study diet in controls:

- a. Family member following physician-prescribed cholesterol-lowering diet (identified by questionnaire at SV1).
- b. Parental history of myocardial infarction before age 45 (identified by questionnaire at SV1).

4. Behavior problems in child or family likely to reduce

adherence:

- a. Truancy (identified by questionnaire at SV1).
- b. Very problematic score on Achenbach (identified by Achenbach test at SV2).
- c. School failure (left back two grades or more) (identified by questionnaire at SV1).
- d. Alcoholic parent (identified by self-reported alcohol consumption on questionnaire at SV1).
- e. Difficulty in scheduling screening visits (local clinic discretion).
- f. Daily use of vitamin or mineral supplements (except for one multivitamin per day and/or up to one gram of Vitamin C per day, identified by questionnaire at SV1).
- g. Meals provided by more than three adults on a regular basis (two or more days/week) and/or adults providing meals unwilling or unable to learn diet modification or unable to provide school lunch from

home (identified by questionnaire at SV1 and local clinic discretion).

h. In special education classes (identified by questionnaire at SV1).

i. History of anorexia and/or bulimia (identified by questionnaire at SV1).

j. History of intentional rapid weight loss or gain (7 lbs. in 2 weeks) or a 5% weight change between SV1 and SV2 (identified by questionnaire at SV1 and by clinical measurements at SV1 and SV2).

k. FS only: Morbid obesity (greater than 175% ideal weight for height) in one or both parents/guardians (identified by questionnaire at SV1, measurements during the screening/baseline period, and local discretion).

l. Parent (who is main food preparer and/or who would attend the DISC intervention sessions) or child non-English reading and speaking (identified by questionnaire at SV1).

5. Other exclusion criteria:

a. Second child in family (enroll both, analyze one).

b. Plan to move more than 50 miles from area within 3 years (identified by questionnaire at SV1).

c. Evidence of beginning sexual maturation (i.e., Tanner stage greater than 1 at SV2).

d. Mean of SV1 and SV2 fasting triglyceride levels greater than 200 mg/dl (approximately the 99th percentile of the triglyceride distribution in this age group). (In FS, fasting triglyceride level of greater than 200 mg/dl at both SV1 and SV2.)

e. Mean of SV1 and SV2 fasting HDL-cholesterol (HDL-C) levels less than 30 mg/dl (approximately the 1st percentile of the HDL-C distribution in

this age group). (There was no exclusion based on HDL-C in the FS.)

f. Dietary fat intake sufficient to allow a margin for intervention (identified by questionnaire at SV1).

g. SV2 is completed less than 3 weeks or more than 8 weeks after the date of SV1, and/or the BV is completed less than 3 weeks or more than 16 weeks after the date of SV1.

4.2 Prescreening Assessment for DISC I

Four Clinical Centers (Johns Hopkins University, New Jersey Medical School, Louisiana State University/Children's Hospital and the University of Iowa) will be screening large, school-based populations. Johns Hopkins University, New Jersey Medical School and Louisiana State University/Children's Hospital will be centrifuging and testing the specimens at the school, using a desktop analyzer (Kodak DT60), while the University of Iowa will be sending the specimens to the University of Iowa Lipid Laboratory for analysis using standard LRC methods. Northwestern University will be screening children both at elementary schools and at pediatrician's offices during school physical exams and during visits for minor complaints, using different desktop analyzers (see Section 5.3.2). The children with TC levels greater than the 75th percentile, as determined from reference to the LRC age-sex specific distributions of TC, will be identified as candidates for further screening visits. The Kaiser Permanente Center for Health Research in Portland, Oregon, will be screening children of families enrolled in the Kaiser Permanente HMO. The children will be asked to come into the Center for screening using the Kodak DT60.

4.3 Screening and Baseline Visits in DISC I

4.3.1 Screening Visit 1

This visit will be required for all children still considered for inclusion into the study after the Prescreening Assessment and should occur within nine months of the Prescreening Assessment. This visit will involve a venous blood sample taken from a child in a fasting state. A child will be considered to be in the fasting state if he/she has ingested only clear liquids for a period of at least 12 hours before the blood sample is taken.

A small quantity, 15 ml, of venous blood will be obtained from each child and, after appropriate preparation, will be sent to the Central Lipoprotein Laboratory for analysis. The Central Lipoprotein Laboratory will process all blood samples for the study to assure standardized and consistent results. The LDL-C level will be determined by formula from the determinations of TC, HDL-cholesterol (HDL-C) and triglycerides (TG). Children whose LDL-C level is between the 70th and the 99th percentile will be eligible to participate in SV2.

At this visit, certain eligibility and exclusion criteria (indicated in Sections 4.1.2 and 4.1.3) will be assessed for each child; children who are potentially eligible according to these criteria and who meet the eligibility criteria for LDL-C levels will be asked to participate in SV2. The criteria which will be assessed at this visit are those which, generally, can be easily ascertained with a questionnaire administered to the parents during the visit or shortly thereafter.

4.3.2 Screening Visit 2

This visit will be required for all children still considered for inclusion into the study after SV1 and should occur approximately one month after SV1.

A blood specimen of 35-40 ml will be drawn from each child and a lipoprotein analysis will be performed at the Central Lipoprotein Laboratory, as in SV1. Additional non-lipid tests will be done at the Central Non-Lipid Laboratory and

the Central Micronutrient Laboratory. Children with an average LDL-C level from both screening visits between the 80th and the 98th percentile will be identified for inclusion in the study.

A physical examination of the child will be performed (see Section 7.2.2), anthropometric and blood pressure measurements will be made on the child, and an Achenbach Child Behavior Checklist, will be administered to one or both parents at this visit. Section 4.1.3 lists the exclusion criteria which will be assessed at this visit. If the child is eligible for inclusion in the study based on the information collected during SV1 and SV2, he/she will be invited to participate in the BV, about one month after SV2. If, at the time of the BV, the child and parents are still interested in participating and informed consent has been obtained, the child will be randomized.

4.3.3 Baseline Visit

The BV will be required for all children still considered for inclusion into the study after SV2 and should occur approximately one month after SV2. At least one of the parents/guardians of the child should accompany the child at either this visit or SV1 or SV2.

Information to be obtained on the child at the BV will include blood pressure and pulse, a physical activity assessment, and three psychosocial tests.

A 24-hour dietary recall will be obtained on the child at the BV and two telephone-administered 24-hour recalls will be obtained within a two-week period following the BV.

Height and weight will be obtained on the parents/guardians at the BV if not already obtained at SV1 or SV2. A blood sample will be obtained from each of the parents/guardians for lipoprotein analyses performed at the Central Lipoprotein Laboratory (FS only). The Family Environment Scale will be administered to at

least one and preferably both of the child's parents/guardians for the child's participation in the randomized trial.

A final assessment of the child's eligibility for the study will be made at the BV. If all of the DISC eligibility criteria are met, the Clinical Center will notify the Coordinating Center as soon as the third 24-hour dietary recall has been obtained. The Coordinating Center will check to make sure that all of the necessary forms have been received for this child, that none of the "INELIGIBLE" boxes have been checked, and that the biochemical determinations from the Central Laboratories all meet the eligibility criteria. The Coordinating Center will then transmit the treatment assignment to the Clinical Center by electronic mail. The Clinical Center will notify the child and parents/guardians of the treatment assignment by telephone and mail. For those assigned to the intervention group an appointment will be made for the first intervention session.

4.4 Informed Consent in DISC I

Obtaining informed consent is an important part of the screening and recruitment procedure in DISC I. The process will begin with parental permissions for the children to participate in the DISC I prescreening assessment. Immediately after the Prescreening Assessment, an introductory letter and information sheet will be sent to the parents of prospective participants, which will include those children identified in the prescreening process as having elevated total cholesterol. A second consent form will be sent to the child's parents/guardians prior to SV1 for permission to carry out SV1, SV2, and BV measurements and interviews on the child. A third consent form will be presented by an interviewer during the BV and will be signed by both the child and his/her parents/guardians. This form will contain an explanation of the randomized trial, information about the intervention and its possible risks, the intervention and examination schedule, steps taken to insure confidentiality and safety, information about later withdrawal from participation, and an offer to answer any questions about study procedures.

Any modifications required by Institutional Review Boards of a local clinical center's consent form may be made by the Principal Investigator of the clinic involved as long as the guidelines established by the Steering Committee are maintained. All final consent forms will be reviewed by the Steering Committee.

4.5 Referral of Ineligibles in DISC I

If a child is deemed ineligible for the study, there will be certain conditions for which a referral to an appropriate health professional will be made or recommended. These conditions are as follows:

1. Hypothyroidism.

2. Nephrotic syndrome.
3. Renal failure.
4. Height less than 5th percentile of the reference distribution.
5. Weight for height less than 5th percentile or greater than 90th percentile of the reference distribution.
6. Systolic blood pressure 125 mm Hg or greater or diastolic blood pressure 80 mm Hg or greater at both screening visits.
7. LDL-C greater than the 98th percentile of the reference distribution.
8. Major behavioral problems.
9. Other medical conditions deemed important by the local investigator(s).

Each local Center may, at its option, offer to provide the care at the center or to refer the child to a local health professional. Each center should have a prepared list of local health professionals who have agreed to see any child with the above conditions.

4.6 Eligibility Criteria for DISC II

All DISC I participants who have signed a DISC II informed consent form covering participation until the child is 18 years old will be eligible for DISC II.

The DISC II consent form will be the fourth consent form presented to DISC participants, and will cover procedures to be performed up to the time that the child is 18 years old. It will be presented by an interviewer at the 36 month DISC I data collection visit, and will be signed by both the participant and his/her parent.

Special efforts will be made to maintain the DISC I cohort into DISC II up to the final data collection visit at the child's age 18. If necessary, consent

forms limited to specific visits or core DISC measures will be offered to those who refuse to give a broader consent.

CHAPTER 5

RECRUITMENT OF PARTICIPANTS

5.1 Goals

Each local Clinical Center is required to recruit and randomize 20 participants for the feasibility study and 80 participants for the full-scale study. Both girls and boys should be equally represented at each center and, as far as possible, a number of non-white children should be recruited.

5.2 Overview of All Centers

The potential respondent universe for the DISC is non-institutionalized males between the ages of 8 years 7 months (8 years 10 months in feasibility study) and 10 years 10 months, or females between the ages of 7 years 10 months and 10 years 1 month (9 years 10 months in the feasibility study) as of the day of Screening Visit 1 (SV1) in six Clinical Centers in Newark, NJ, Baltimore, MD, New Orleans, LA, Chicago, IL, Iowa City, IA, and Portland, OR. A window of two weeks on either side of the day of SV1 was allowed for satisfying the age eligibility criteria. Clinical Centers will identify eligible children through the series of screening visits described in Chapter 4. Four of the Centers (Newark, Baltimore, New Orleans and Iowa City) will perform the prescreening primarily in elementary schools. One of the Centers (Chicago) will perform the prescreening partly in elementary schools and partly in the offices of pediatricians in a large pediatric research group. The sixth Center (Portland) will be screening children of families enrolled in the Kaiser Permanente HMO in the Portland area.

Specific recruitment strategies employed by the six Clinical Centers for recruiting schools and proposed approaches for recruiting children are discussed in the following sections.

5.3 Specific Strategies for Clinical Centers

5.3.1 Johns Hopkins University

The following recruitment strategy will be employed by the Johns Hopkins DISC Clinical Center. There are 92 elementary schools in the Baltimore County school districts, with a total enrollment of approximately 16,359 pupils (8,438 boys, 7,921 girls) in the third, fourth, and fifth grades. Using a computer printout from the schools, the pages were numbered sequentially and each school assigned a number. Using a random number table, 10 schools were chosen for the purposes of cholesterol screening for the feasibility study. Additional schools will be randomly chosen as needed for the purposes of the full scale study.

Based on data from September 1986, an estimate of breakdown of the schools for September 1987 is 73.7 percent white and 26.3 percent black. Two of the schools have greater than 50 percent black enrollment. We estimate that there are 1,133 eligible children for the purposes of cholesterol screening for the feasibility study.

5.3.2 Northwestern University

Children potentially eligible for DISC will be identified via pre-screening in offices of pediatricians in the Pediatric Practice Research Group (PPRG).

In two practices, desktop fingerstick screening for nonfasting total cholesterol will be done on children in the eligible age range who present for routine care (school physical or minor complaint) during the period June 18-October 15, 1987. One practice will use a Seralyzer machine, the other a Clay-Adams machine. After obtaining parental consent, fingerstick blood will be drawn and spun; serum will be frozen for weekly total cholesterol (TC) determinations. The results of these, along with a log of all patients seen, will be provided to the PPRG office on a weekly basis. TC results will be mailed to the parents in

accordance with DISC procedures. Children with prescreen TCs at the 75th percentile or more of the reference distribution will be recalled in September and October for lipid screening in the DISC laboratory.

In other practices, some potentially eligible children identified by other types of lipid determination will be referred to the PPRG for DISC screening. This is likely to occur in one of two ways: two PPRG pediatricians routinely obtain fasting TC, HDL/Cholesterol, and triglyceride measures on their patients; others receive the results of blood tests done for other reasons (e.g., postoperative). For nonfasting values, the same cutoff for DISC screening will be used as for the practices prescreening for DISC as described above. For fasting values, the threshold for DISC screening will be the 80th percentile.

5.3.3 University of Iowa

Children who are potentially eligible for DISC feasibility trial will be identified via pre-screening in the schools of Clinton and Muscatine, Iowa. These school districts are predominantly white. Recruitment will begin by sending home a letter and brochure from each classroom along with a consent form for pre-screening. The consent forms are to be returned to each classroom teacher. These permission slips will be gathered, and those students not returning consent forms will have a mailing sent to their homes of the identical material previously taken home by the children with a return self-stamped, self-addressed envelope to our study center. On the day prior to screening, a reminder will be sent to each classroom teacher involved identifying the children to be examined.

In Muscatine, Iowa the pre-screening has been completed as part of the ongoing Muscatine Study. Venous bloods have been drawn from the children and the analyses carried out in the Lipid Research Center laboratory for total cholesterol and triglycerides. Heights and weights of these children have also been obtained.

In Clinton, beginning in the fall of 1987, the children will be sampled utilizing the Kodak DT-60 Analyzer for total cholesterol.

By these techniques the Center anticipates contacting approximately 1,000 students, with approximately a 70% participation rate for the pre-screening. It appears that eight to ten schools will need to be contacted to supply the required number of students of appropriate age.

5.3.4 Louisiana State University/Children's Hospital

The DISC recruitment strategy incorporates the procedures used in other school-based screenings conducted over the past 15 years, particularly the Bogalusa Heart Study.

A total of 76 schools are available in the Archdiocese of New Orleans. Schools are contacted initially by a letter, after receiving approval from Howard Jenkins, superintendent of schools. Seventeen schools on the west bank of the Mississippi River were eliminated due to their lack of proximity to the clinical site. Of the remaining 59 schools, 33 have been classified as predominantly white student body and 26 predominantly black. Of these schools, 41 are located in Orleans parish (county) and 18 in Jefferson parish. Five predominantly white schools are contacted for each predominantly black school to assure the appropriate racial balance, i.e., 10-15% black. One week later, a telephone contact is made to set-up a session with the principal to explain the rationale and scope of the study and recruit the school to participate. After permission is granted, the school is requested to furnish the center with census information on 3rd, 4th and 5th grades and the school calendar for 1987-1988. For the feasibility study, this phase began in April 1987.

Early in the fall, the schools will be recontacted. A parent meeting will be scheduled in conjunction with the fall meeting of the parent-teacher

organization to explain the program and answer any questions or concerns. A similar meeting will be held with each school faculty to enlist their support. Similarly, a presentation is planned at a system-wide meeting of principals. Approximately three to four weeks prior to screening, an initial consent letter will be distributed via the classroom teacher. The next week a follow-up letter will be sent to parents of children who did not return consent. The day prior to screening, a reminder will be sent to the classroom teachers involved, identifying the children to be examined. The center anticipates contacting 1,000 students with approximately 65-90% consenting to screening. It appears that 8-10 schools will be needed to supply the required number of appropriate aged students.

5.3.5 New Jersey Medical School

The DISC Center at the New Jersey Medical School in Newark will center its recruitment plans around screening at school sites. While a total population of over 30,000 children in the 8-10 age group were identified in the original grant application, it is planned to concentrate recruitment for the feasibility study in two school systems, Union Township and Montclair, with over 2,000 children in the DISC age range. After return of consent forms by parents, screening through fingerstick samples will take place at the schools, with cholesterol determinations on the Eastman Kodak DT60, if possible, at the screening site. In addition, letters will be sent to pediatricians participating in health maintenance organization soliciting referrals for screening in the clinic, and volunteers for such screening will be sought through press releases and other media coverage. Participants in other studies, such as the Trials of Hypertension Prevention, will be informed of the availability of free screening, as will private patients in the preventive cardiology program and those contacted during

recruitment for the Trials of Hypertension Prevention. These same strategies will be extended and utilized for the full-scale trial.

5.3.6 Kaiser Permanente Center for Health Research

(To be written)

CHAPTER 6

RANDOMIZATION AND TREATMENT ALLOCATION IN DISC I

6.1 Eligibility Assessment, Treatment Allocation, and Entry into the Study

Prospective DISC participants will have a prescreening assessment plus two screening visits (SV1 and SV2) and a baseline visit (BV) at which blood will be drawn for lipoprotein determinations. At these visits assessments will be made of a child's eligibility with respect to medical conditions affecting growth and/or cholesterol levels, use of medication that may affect lipids, factors likely to increase adherence to study diet in control participants, behavior problems, and other factors. The data forms reporting the results of these assessments will be sent to the Coordinating Center where they will be checked for completeness and compliance with the DISC eligibility and exclusion criteria. A final assessment of the child's eligibility for the study will be made at the BV. If all of the DISC eligibility criteria are met, the Clinical Center will notify the Coordinating Center as soon as the third 24-hour dietary recall has been obtained (generally within two weeks following the BV). The Coordinating Center will then make a final check to make sure that all of the necessary forms have been received for this child, that none of the "INELIGIBLE" boxes have been checked, and that the biochemical determinations from the Central Laboratories all meet the eligibility criteria. The Coordinating Center will then transmit the treatment assignment to the Clinical Center by electronic mail. The Clinical Center will notify the child and parents/guardians of the treatment assignment by telephone and mail. If assignment has been made to the intervention group, an appointment will be made for the first intervention session. The transmission of the treatment allocation from

the Coordinating Center to the Clinical Center marks the child's official entry into DISC. This means that the child will be included in the DISC data analyses even if he/she decides the next day to drop out of the study.

6.2 Randomization Procedure

Separate randomization schedules for each of four age-gender strata within each of the six DISC Clinical Centers will be computer-generated at the Coordinating Center. The age-gender strata are: 8-year old females, 9-year old females, 9-year males, and 10-year old males. Each schedule will be designed to provide approximate balance in the number of participants assigned to the intervention and control groups within each stratum throughout the enrollment period. This will be accomplished using a procedure similar to those described by Efron,¹ Pocock and Simon,^{2,3} and Wei⁴ in which the probability of allocation to one group or the other varies according to the degree of imbalance already existing within the particular stratum. Thus, for example, a probability of .5 of assignment to either treatment group will be used for the next allocation if equal numbers have been assigned to the two groups at a given point. However, a probability of .4 might be used for assignment to the intervention group and .6 for the control group if, say, there are two more participants assigned to the intervention group than the control group at a given point. More extreme probabilities will be used for larger imbalances.

Each of the 24 randomization schedules will contain sequences of at least 50 allocations, twice the number expected for each stratum. These schedules will be used by Coordinating Center staff in preparing treatment allocation assignments.

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May 10, 1995

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CHAPTER 7

DATA COLLECTION AND PRIORITIES

7.1 Lipid and Lipoprotein Measurements

Inasmuch as an assessment of the effect of dietary treatment on blood lipids, lipoproteins and apolipoproteins will be a measure of the efficacy of dietary treatment, the following measurements will be made in DISC I and DISC II study subjects: total cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL-C), LDL-C (calculated from a modified Friedewald equation in which VLDL is estimated as TG/X , where $X = 6.5$ for children and 6.3 for adults, derived from the Lipid Research Clinics (LRC) Prevalence Study data), apolipoprotein A-1 (apo A-I) and LDL apolipoprotein B (apo B). These measurements will be performed in a Central Lipoprotein Laboratory at Johns Hopkins University which is standardized for TC, TG and HDL-C measurements according to criteria of the CDC-NHLBI Lipid Standardization Program. The measurements will be made in serum that will be collected at the Clinical Centers, separated into aliquots of appropriate size, and sent on dry ice to the Central Lipoprotein Laboratory. In DISC I, serum cholesterol ester linoleate:oleate ratio will be determined at the Central Micronutrient Laboratory at the Centers for Disease Control in Atlanta. This dietary adherence measure will be done initially at SV2 in the feasibility study (FS), with a decision to be made later whether to extend this measure to later follow-up visits in the FS as well as to the full-scale trial (FST). Blood samples will be collected as follows. Initially the children will be evaluated for TC, and those whose TC exceeds the 75th percentile of the reference distribution will be invited to participate

in the screening visits. The prescreening cholesterol measurements will be made locally at all six Clinical Centers. Four Centers will analyze fingerstick samples with the Kodak DT-60 device and two Centers will use other methods. These cholesterol values will be used only to identify likely candidates for the study and the values will not be used to establish pretreatment baseline cholesterol levels. Following the prescreening assessment, participants will be brought into the clinic for Screening Visit 1 (SV1) and Screening Visit 2 (SV2). At both screening visits, a blood sample will be obtained after a 12-hour fast for the measurement of TC, TG and HDL-C. Aliquots of serum from SV1 and SV2 will be stored frozen at the Central Lipoprotein Laboratory for determination of apo A-I and apo B on only those children who are randomized into the trial. Follow-up fasting blood specimens will be collected at 6 months (FS only), 12, 36, and 37 months, Year 5, Year 7, Year 9, as well as at the final visit (FV01) and a final visit repeat (FV02) for shipment to the Central Lipoprotein Laboratory for the measurement of TC, TG, HDL-C, apo A-I, apo B and a calculation of estimated LDL-C concentration. The 36-month LDL-C result will be averaged with the 37-month result and the final visit and final visit repeat results will be averaged to provide more stable primary efficacy outcome measures.

The parents/guardians of DISC I children randomized into the intervention group will give a blood sample at the first intervention session for the measurement of TC, TG, HDL-C, apo A-I, and apo B, and calculation of LDL-C. The same determinations will be made on parents/guardians in both the intervention and control groups at the 36-month DISC I follow-up visit. (In the FS blood samples were taken on all parents/guardians who attended the BV, but the serum was put into long-term storage for analysis at the time of the 36-month visit.)

Each time a venous blood sample is taken from a child or parent/guardian for Central Lipoprotein Laboratory determinations in DISC I before the 36-month visit, a drop of the blood sample will be analyzed for total cholesterol using the DT-60 at the DISC Clinical Center and this value will be given to the participant. (In the FS, however, this was not done for the BV blood sample from parents/guardians.) Additionally, intervention group participants--children and their parents/guardians alike--will be given the opportunity to have their total cholesterol measured periodically during intervention sessions using the DT-60 analyzer. Laboratory MN36 lipid determinations on children will also be returned to participants before the beginning of DISC II follow-up visits.

The decision to make lipid and lipoprotein measurements on serum rather than plasma took several considerations into account. First, the LRC data were obtained from fasting plasma samples and give some idea of prevailing lipid and lipoprotein concentration in the U.S. population. It is recognized, however, that the LRC data are not actually from a random subset of the U.S. population. On the other hand, the much larger data set that is being collected from the ongoing National Health and Nutrition Examination Surveys (NHANES) are being conducted in frozen serum samples and, beginning with the upcoming NHANES III survey, will include measures of apo A-I and apo B. Furthermore, beginning with NHANES II conducted in the 1970's, Hispanic HANES, which was conducted in the mid-1980's, and continuing into NHANES III, which will begin in 1987 and be completed in the early 1990's, all of the lipid and lipoprotein analyses will have been performed with CDC standardized methods for TC, TG and HDL-C. Therefore, it is felt that the adoption of similar procedures will allow the data collected in the DISC to be more readily compared with

national population-based data. Second, the use of frozen serum is expected to minimize technical difficulties that might develop in the event that the analyses are delayed due to laboratory or other logistical problems during the course of the study.

Training sessions will be held in which clinic personnel are taught how to collect, process, store and ship study samples to the Central Lipoprotein Laboratory. The use of a common sample handling protocol in all of the Clinical Centers as well as the performance of lipoprotein analyses in a single laboratory will minimize various sources of analytical variability. Provision will be made for repeating the training sessions annually, if necessary, for the benefit of new personnel who may join the study and as a refresher course for continuing personnel.

7.2 Clinical Assessment

7.2.1 Medical History

Medical and social history information will be obtained by standardized questionnaires on several occasions. At SV1, a questionnaire administered by DISC clinic staff will cover historical factors which might result in exclusion from DISC. Early ascertainment of these factors will reduce needless phlebotomy and other assessments on children not eligible for DISC for reasons established by medical history. This questionnaire will cover the following areas.

1. Medical conditions which may affect growth and/or cholesterol level (if present, the child will be referred for treatment):
 - a. Nephrotic Syndrome.
 - b. Liver Disease.
 - c. Diabetes Mellitus.
 - d. Inflammatory bowel disease (Crohn's or ulcerative

colitis).

e. Renal failure.

2. Medications which may affect lipids, growth, or other outcome measures:
 - a. Thiazide diuretics.
 - b. Retinoids.
 - c. Steroids.
 - d. Lipid-lowering medications.
 - e. Ritalin.
 - f. Phenobarbital.
 - g. Dilantin.
 - h. Therapeutic iron.
 - i. Thyroid medication.
3. Factors likely to increase adherence to the study diet in controls (compared to intervention children):
 - a. Parent on physician-prescribed fat-modified diet.
 - b. Parental history of myocardial infarction before age 45.
4. Behavior or other problems in child or family likely to reduce adherence to the diet:
 - a. Truancy.
 - b. Left back in school two grades or more.
 - c. Alcoholic parent.
 - d. Use of vitamin or mineral supplements.
 - e. Meals provided by more than three adults on a regular basis (two or more days/week) and/or adults providing meals unwilling or unable to learn diet modification or unable to provide school lunch from home.
 - f. In special education class.
 - g. History of anorexia nervosa and/or bulimia.
 - h. History of intentional rapid weight loss (seven pounds or more in two weeks).

- i. Weight of parents/guardians over 175% ideal weight for height (FS only).
 - j. Parents and/or child non-English speaking.
- 5. Other
 - a. Plans to move more than 50 miles from area within three years.
 - b. Greater than Tanner Stage 1.

A more extensive self-administered questionnaire will be sent to the parents/guardians prior to SV2 to collect data for DISC enrollment.

The SV2 parent history will include the following:

1. Identity, place of residence, education and occupation of parents/guardians.
2. Race.
3. Household composition: number and ages of all individuals living in household.
4. Place and type of residence.
5. Family income.
6. Additional medical history on child: hospitalizations, operations, days school missed.
7. Family medical history: angina, MI, coronary bypass surgery or angioplasty, high cholesterol, hypertension, diabetes.

Parents will be asked to update their child's medical history at annual follow-up visits. Beginning in Year 06, when participants will be 15 and 16 years of age, the medical history will be completed by either the participant or a parent. Also beginning around Year 06, parents will no longer be asked to supply information about girls' menstrual cycle, contraceptive use, and pregnancy.

In addition, a child history questionnaire will be administered to the child at SV2 and at annual follow-up visits to ascertain

information only he/she may have. This form will ask about the following:

1. Alcohol/drug use.
2. Cigarette use.
3. Use of contraceptives (not SV2).
4. Use of steroids (not SV2).
5. Pregnancy (not SV2).

7.2.2 Physical Examination

A physical examination on DISC children will be performed at SV2 and at annual follow-up visits. The purpose of the initial physical examination before randomization (SV2) is to establish that each child meets the medical eligibility criteria for inclusion in DISC and serves as a baseline medical evaluation for each participant. This examination should reveal a generally healthy prepubescent child (Tanner Stage 1).

Follow-up physical examinations on DISC study children are intended to assess their general physical health, growth and maturation during the course of this study. Special attention will be given to their nutritional status. The purpose of these examinations is to monitor the safety of the dietary intervention and to provide information on study end points.

These examinations will be brief but complete, lasting approximately 10-15 minutes. During this study children will present with acute illnesses, such as otitis media, pharyngitis, asthma, bronchitis, and pre-existing chronic problems such as scoliosis, inguinal hernia, or a significant heart murmur. Beginning at the 36 month annual follow-up visit a screening question for practices associated with eating disorders will be administered. The question,

together with changes in body mass, will be used to identify possible cases of anorexia or bulimia in DISC participants. These conditions may require evaluation, treatment and/or follow-up and should be referred to the child's usual health care provider.

The physical examination of DISC children will be performed by either a pediatric nurse practitioner, a child health associate, or a pediatrician. Whenever possible, the examiner will remain the same for each child throughout the study and, if possible, he/she will be the same gender as the study child.

The examination will briefly cover the child's general appearance, head, ears, nose, mouth, teeth, eyes, neck, chest, lungs, heart, abdomen, genitalia, musculo-skeletal system, nutritional status and note the presence of active infections.

7.2.3 Tanner Staging

An assessment of pubertal development will be made on each DISC child at SV2 and at each annual follow-up visit until the child has reached Tanner stage 5. One purpose of the initial (SV2) evaluation is to establish that the child is prepubescent. Evidence of beginning sexual maturation is an exclusion criterion from this study.

Female pubertal development will be assessed by evaluating breast and pubic hair development. Male pubertal development will be assessed by evaluating genitalia and pubic hair development and measuring testicular volume. These observations will provide data on the initiation and progression of pubertal development in the DISC population.

The assessment of pubertal development on DISC children will be performed by either a pediatric nurse practitioner, a child health associate, or a pediatrician. Whenever possible, the examiner will

remain the same for each child throughout the study and, if possible, he/she will be the same gender as the study child.

7.2.4 Menstrual History in Girls

As part of the physical exam, questions about menarche will be asked at all clinic visits until girls have started to menstruate. Beginning at the 36 month clinic visit, girls who have reached menarche will complete menses calendars for six weeks before and six weeks after each clinic visit that includes a blood draw.

7.2.5 Anthropometry

Height and weight will be obtained on the child participants, wearing hospital gowns, at SV2 and at each annual follow-up visit. Triceps, subscapular and suprailiac skinfolds and arm, waist, hip (bitrochanter), and maximum below waist circumferences will be measured on children at SV2 and at 12 months, 36 months, and at the final follow-up visit.

Weight will be measured using a Health-o-Meter electronic scale and skinfolds will be measured using Tanner-Whitehouse (Holtain) skinfold calipers. Each of these measurements can be made twice by the same observer. A third measurement will be made if the second measure differs from the first measure (by the same measurer) by more than 0.2 kg for weight, 1 mm for each of the three skinfolds, 0.5 cm for arm circumferences, or 1.0 cm for the waist and hip circumferences.

Height will be measured using a special-order stadiometer. For height, measurements will be performed once each by two observers. The second height measurer will be blinded to the results of the first measurement. A third measurement will be made if the second measure differs from the first by more than 0.5 cm. The mean of the two closest height measurements will be used for data analysis purposes.

See the DISC Manual of Operations Chapter 10 for detailed anthropometric measurement procedures.

For eligibility purposes, single measurements of height and weight will also be taken at SV1 and weight at SV2 with the child in street clothes.

For adults, height and weight will be measured during the baseline period and at the 36-month follow-up visit. Each measurement will be made once.

Each center will designate a primary and back-up anthropometrist.

Central training will be followed by weekly practice measurements performed by the anthropometrists at their respective centers, with documentation to be forwarded to the trainer for evaluation. Certification of anthropometrists will be done annually. Quality control of anthropometry will be based on duplicate measurements of 10% of the participants measured in each examination cycle.

7.2.6 Blood Pressure and Pulse Measurements

Systolic and diastolic (fourth and fifth phase) blood pressures will be measured in children at SV2, BV, 12, 36 months and at the final DISC II visit. Prior to taking blood pressure measurements, the right arm circumference will be measured in order to select the appropriate blood pressure cuff size. Two blood pressure measurements will be taken at 60 second intervals, with the child in a sitting position, using a Baum random zero mercury sphygmomanometer. In general, both measurements will be made by the same person. The mean of the two measurements will be used as the child's blood pressure for that exam.

For a 10% sample of the children, a second blood pressure measurer will take an additional set of blood pressure readings for quality

assessment purposes. A 30-second pulse rate will be measured once, between the two blood pressure readings.

7.2.7 Nonlipid Laboratory Tests

7.2.7.1 Introduction and Tests To Be Performed

A number of nonlipid laboratory tests will be done at SV2, at 12 and 36 months, and at the DISC II final visit. At these visits, 35-40 ml of blood will be drawn; hemoglobin and hematocrit determinations will be done locally, while other determinations will be done centrally. (In the FS, additionally, a urine sample was obtained for dipstick protein analysis, and a complete blood count and cell indices were determined locally.) Serum and red cell hemolysate will be frozen and sent to the Central Lipoprotein Laboratory at Johns Hopkins University. A portion of the serum will be used by that Laboratory for lipoprotein and apolipoprotein determinations; another portion will be sent to the Central Non-Lipid Laboratory at Johns Hopkins University for determinations of serum T4 and components of a standard chemistry panel. The remaining portion of serum and the red cell hemolysate will be sent to the Central Micronutrient Laboratory at the Centers for Disease Control in Atlanta for determinations of serum retinol, tocopherol, five carotenoids (alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene), ferritin, zinc, copper, and red cell folate.

Tests to be performed can be grouped according to three major objectives:

1. Assessment of presence of specific exclusion criteria: serum albumin, SGPT (or alanine amino transferase), fasting serum glucose, and serum T4 (thyroxine).

2. Assessment of the primary and secondary nutrition safety outcome measures: hemoglobin, hematocrit, serum ferritin, zinc, copper, retinol, tocopherol, and carotenoids, red cell folate, and albumin.

3. Assessment of changes over time in additional components of a standard chemistry panel, including serum urea nitrogen, creatinine, total and direct bilirubin, calcium, phosphorus, uric acid, total protein, SGOT (or aspartate amino transferase), and alkaline phosphatase.

All tests in the second group plus albumin will be done at SV2 and at 12 and 36 months and at the final visit. Additionally, SGPT, glucose, and the tests in the third group will be done at SV2 and 36 months. T4 is mainly an exclusionary test and done only at baseline. The likelihood of new hypothyroidism is considered too low to warrant reassessment during follow-up. Non-lipid laboratory tests will not be done on parents/guardians.

Beginning in DISC I at the 12 and 36 month visits and continuing in DISC II at the Year 5, 7, 9 and final visits, a number of hormone determinations will be performed on serum samples for both male and female children. At SV2 and at the 12 month visit, 2.5 ml of serum will be collected for hormone analyses from participants who have not completed these visits prior to the initiation of the hormone study. At the 36 and 37 month visits, 2.5 ml of serum will be collected from all participants. At the Year 5, Year 7, Year 9, and the final visits, 5 ml of serum will be collected from all participants for hormone analyses. See Chapter 9A for the rationale and details of tests to be performed. Beginning in DISC II at Year 7, a one-time sample of 5 ml of whole blood will be drawn from participants at an annual or final

visit for DNA analyses (DNA Ancillary Study). See Chapter 13, Exhibit 13.2 for the rationale and tests to be performed.

7.2.7.2 Rationale

The measurements of SGPT and albumin serve several purposes. Hypoalbuminemia can be an indicator of protein-calorie malnutrition, and SGPT and albumin can serve as screening measures for infection and/or liver disease. Finally, the albumin level may be correlated with and affect the serum zinc level, which will also be measured.

Serum glucose will be used to exclude those with diabetes. Thyroxine will be measured and in the few cases of values below a lower cutpoint, thyroid stimulating hormone will be determined to rule out hypothyroidism. Because hypothyroidism is so infrequent, it is extremely unlikely that a child with hypothyroidism will be randomized in DISC if the T4 is normal.

The second group of tests listed in the preceding section is being done to obtain objective assessments of the nutritional status of participants. Iron and zinc status will be assessed because these are the nutrients for which dietary data indicate the greatest likelihood of borderline deficiency in cholesterol-lowering diets. Iron status will be evaluated by the hemoglobin and hematocrit indices and serum ferritin. These are considered sufficient to establish safety and identify long-term changes in iron status. Although longitudinal tracking of ferritin levels in children this age is not established, the test can be accurately and precisely done and is considered the best measure of long-term changes in iron stores. Ferritin was therefore chosen as the primary nutrition safety outcome measure and

blood will be drawn for ferritin assay on each child after ascertaining that the child is not acutely infected at the time of the clinic visit.

Hemoglobin and hematocrit are included as confirmatory measures of iron status.

There are no tests currently accepted as adequate to assess zinc status. Even though nutrient analyses of the DISC dietary intervention consistently find zinc to be the nutrient most likely to be deficient relative to the RDA, zinc was not chosen as the primary nutrition safety outcome measure in DISC because of the lack of specificity of hypozincemia. However, because of the potential zinc deficiency in the diet, it was felt important to evaluate zinc status as well as possible. Group differences in serum zinc levels could be meaningful.

DISC staff will standardize the interval from eating to phlebotomy, assess the possibility of infection, measure serum albumin and alkaline phosphatase, and also measure serum copper in order to reduce the effect of artifacts in serum zinc measurements and to maximize specificity of the assay.

Serum retinol and red cell folate will be determined as possible measures of a positive effect of the new dietary pattern, since it encourages an increase in vegetable consumption. In addition, because 28% fat, while not extremely low, does represent a decrease from the average child's diet in the United States, it is felt desirable to assess the status of fat-soluble vitamins. Measurement of retinol and tocopherol serves this purpose.

7.3 Psychosocial Assessment

7.3.1 Introduction

Psychosocial assessment in DISC is designed to implement the two primary DISC goals. These are to demonstrate that the DISC diet is

safe for children in the 8 to 18 year age group, and that it is effective in lowering LDL-C in children at risk. Accordingly, the goals of psychosocial assessment in DISC are the following:

1. To demonstrate the safety of the DISC intervention and control group diets regarding the cognitive, behavioral, attitudinal, and social functioning of children in the intervention group.

2. To identify cognitive, behavioral, attitudinal, and social factors which p

The first task of psychological monitoring in DISC is to test the hypothesis that dietary intervention is safe, i.e., that children are not harmed by being identified and placed on a reduced fat cholesterol diet. Four major types of indicators will be used in DISC to provide information about participants' developmental progress: indicators of cognitive development, behavior problems, attitudes and emotions, and family environment. Each type of indicator will be important for assessing potential dietary or screening effects of the DISC program. No single area is sufficient in and of itself.

The general types of psychosocial safety monitoring indicators in DISC II will remain essentially unchanged in order to provide for continuous psychosocial safety monitoring from recruitment at ages 9 and 10 to age 18. However, some changes in emphasis and in the methods used for psychosocial safety monitoring are appropriate for adolescent participants. Concerns have been raised about increases in morbidity resulting from suicide, violence, and accidents in an adult population enrolled in cholesterol reducing clinical trials. Therefore, increased emphasis will be given to monitoring for behavior and related adjustment problems in adolescent DISC II participants.

Other changes in DISC methodology will be necessary due to the increased literacy and independence of DISC participants after age 15.

Standardized psychological scales for children used during DISC I will

be changed to age appropriate versions for young adults. Self-reported adolescent behavior problems will be gathered in addition to parental reports of adolescent behavior problems. Alternative methods of psychosocial data collection by mail or phone may be developed in order to minimize possible missing data at the final data collection visit.

7.3.1.1 Cognitive Development

The Woodcock-Johnson Math and Reading Clusters¹ are standardized math and reading achievement tests suitable for use from age 3 to 65 years. Math and reading achievement subtests will be used in the DISC I and continued in the DISC II battery because of the key role these subjects play in over-all academic performance before high school graduation. Reading subtests to be used are letter-word identification, word attack, and passage comprehension. Math subtests chosen for administration are calculation and applied problems. Normative data were collected from a sample of 4700 nationwide, with subjects stratified by gender, race, occupational status, geographical region, and type of community.

7.3.1.2 Behavior Problems

Problems reported by parents constitute another meaningful source of information about children's progress. In younger DISC I participants, these natural observers will be able to judge how their child is doing at mastering basic social-developmental challenges involved in becoming more independent, expressing feelings in appropriate ways, interacting with others, and taking part in his or her social group. Because parents are with the child over prolonged periods, their reports provide information not captured in a brief test. A variety of problem behavior rating scales have been developed for teacher and parent use; the best of these is the Achenbach Child

Behavior Checklist (CBCL).² CBCL subscale scores indicate the degree to which a child is manifesting high levels of internalizing problem behaviors (acting withdrawn, avoidant, depressed) or externalizing problem behaviors (acting aggressive and openly angry). The CBCL also can be used to measure the child's level of social competence, i.e., how well he or she does at making friends and being part of a social group.

To monitor behavior problems in older DISC II participants, the Youth Self-Report³ will be used in addition to the parental report. This is a standardized instrument which parallels the Achenbach Child Behavior Checklist used for parents. It is a self-report measure for ages 11 to 18 yielding scores for total behavior problems, internalizing and externalizing problems, as well as individual subscale scores.

7.3.1.3 Self-Reported Attitudes and Emotions

Children often have difficulty putting threatening feelings into words, however they can report their inner emotional states if the questions are phrased carefully in a non-threatening context. Children's self-reports provide unique and important information about fears and worries, and are invaluable aids to detecting conditions such as depression or anxiety. Because DISC screening and intervention could engender fear or self-doubt, reliable and interpretable measures of these emotions will be included in the DISC safety assessments.

To monitor depression, the Kovacs Child Depression Inventory⁵ (DISC I) and the Beck Depression Inventory⁶ (DISC II) will be used. These are well-known 21 and 27 item scales for assessing depression in children and adolescents that are well correlated with other depression scales and clinical ratings of depression. Measurement of depression

in adolescents is particularly important because of concerns raised about suicide. The Children's Depression Inventory used in DISC I is a downward extension of the Beck Depression Inventory for adolescents and adults.

To monitor anxiety, the Spielberger Trait Anxiety Inventory⁷ (Children's version in DISC I and adult version in DISC II) will be administered. These are one page trait anxiety inventories which are widely used and well standardized instruments.

7.3.1.4 Family Environment

To monitor the effect of intervention and the diet on the family environment, the Family Environment Scale⁸ (Moos) will be administered in DISC I and II. The instrument has been used in studies of stress and depression in community samples, and in measures of chronically ill children. Subscales include: cohesion, expressiveness, conflict, independence, achievement orientation, intellectual-cultural orientation, moral-religious orientation, organization, and control. Second order factors of support, conflict, and control have also been identified.

7.3.2 Summary of the DISC Psychosocial Assessment Battery

Safety of the DISC diet for children will be monitored in four areas of general concern: cognitive development, behavioral adjustment, self-reported emotions and attitudes, and family environment. In each area, we have reviewed the most widely used measures and have selected the instrument with the best track record for reproducibility and utility for developmental monitoring. Selection of specific instruments was based on suitability in terms of age and literacy requirements. Attention was also given to the length of forms, methods of administration, and cost to the project.

7.3.2.1 Monitoring Psychosocial Safety of the Diet

1. Woodcock-Johnson Math and Reading Clusters¹ (25 minutes).

Administered to child by trained technician at baseline and 12-month, 36-month and final follow-up visits. Measures child's mastery of math and reading skills. (DISC I and II)

2. Achenbach Child Behavior Checklist (CBCL)² (20 minutes). This

will be administered to at least one and preferably both parents at SV2 and 12 months, 36 months, and the final visit.

Parents can complete this paper and pencil questionnaire at home or while waiting at the clinic. The CBCL includes indices of internalizing behavior (withdrawal, avoidance, shyness), externalizing behavior (anger, aggression, non-compliance) that might occur in response to DISC labeling and diet, as well as social competence (ability to interact with others and make friends) which might also be affected. (DISC I and DISC II)

3. Youth Self-Report³ (Achenbach, 1988). Parallels the CBCL used in DISC I and II for ages 11 to 18. (DISC II) Final visit only.

4. Kovacs Child Depression Inventory⁵ (CDI) (10 minutes). The

technician administers this to the child at baseline and 12 and 36 months. The CDI picks up feelings of low self-worth, hopelessness, or indicators of depression that could occur in response to being placed on an unusual diet. (DISC I)

5. Beck Depression Inventory⁶ (Beck and Steer, 1987). Adult form of the CDI used in DISC I. Administered at the final visit. (DISC II).

6. Spielberger Trait Anxiety Inventory⁷ (STAI-C2 Children's version) (10 minutes). The child will complete this at

baseline and 12 and 36 months. The STAI-(C2) provides a reliable indicator of the child's usual or trait level of fear or anxiety. (DISC I)

7. Spielberger Trait Anxiety Inventory⁷ (Spielberger, Gorsuch, and Lushene, 1970). Adult form of the STAI administered at the final visit. (DISC II)

8. Moos Family Environment Scale (FES)⁸ (25 minutes). One or both parents will complete this paper and pencil questionnaire while waiting at the clinic at baseline, 12 months, 36 months, and the final visit. The FES measures aspects of family structure, interaction, and climate that could be affected by participation in DISC. (DISC I and II)

7.3.2.2 Predicting Compliance to Diet

In addition to monitoring safety, the psychological assessment will assist in identifying behavioral and social factors that influence the degree to which families adhere to the recommended diet. For example, children with higher scores on the CBCL, CDI, or STAI could do less well when asked to comply with the DISC diet. An important outcome of DISC will be to suggest normative guidelines for identifying children and families in which diet interventions are likely to succeed. Three other important predictor variables qualify as compliance measures: the degree to which parents appear to have been successful in managing the child's behavior in the past, the number and severity of stressful life events experienced by the family at baseline, and the family's basic socioeconomic resources. Instruments to assess these variables will be administered in DISC I on a take-home basis at the beginning of intervention, and will only be completed by families in the intervention group. Socioeconomic status will be

obtained from both intervention and control group families prior to randomization.

The following instruments will be used in DISC I to predict compliance to diet:

1. Eyberg Child Behavior Inventory⁹ (10 minutes). Administered at the first intervention session (intervention group only). Measures degree of influence parents have been able to establish over the child's behavior, as reflected in behavioral compliance problems and signs of immaturity.
2. Sarason Life Experiences Scale¹⁰ (20 minutes). Administered separately to both parents at the first intervention session (intervention group only). Parent reports stressful events occurring in recent months. This could be important for predicting noncompliance or tendency to drop out of the intervention.
3. DISC Household Information Form (10 minutes). Sent home prior to SV2 for completion by a parent (both intervention and control groups). Gathers information on socioeconomic status in the form of occupation, education, and income of both parents; household composition; and ethnic group affiliation. Demographic information will also be important for describing the sample of DISC participants and comparing findings to data from other studies. Table 7-1 summarizes the forms used for monitoring dietary safety and predicting dietary compliance.

7.3.3 Validation of Psychosocial Instruments

Previously published instruments chosen for DISC have already demonstrated construct validity. For most of these instruments age,

gender, and race specific norms are available. Data from the DISC population of high-LDL children will be compared to published norms to determine whether results are consistent with those from prior investigations.

7.3.4 Time Required to Complete Psychosocial Assessment

Table 7-2 shows the estimated time requirements for parent and child to complete the psychosocial questionnaires at each visit. In DISC I, children and their parents will be asked to spend approximately 45 minutes completing study psychosocial questions at the baseline, 12 and 36 month visits. In DISC II, questionnaires will take about 65 minutes for children and 45 minutes for parents to complete at the final data collection visit.

7.4 Dietary Assessment

7.4.1 Objectives

Measurement of dietary adherence in DISC will provide the basis for evaluating the efficacy, safety and feasibility of dietary intervention after 36 months (DISC I) and at age 18 (DISC II). The overall objectives of dietary assessment in this study are:

1. To ensure that the intake of dietary fat at baseline provides a margin for change.
2. To estimate usual individual intake for establishing baseline dietary patterns and to monitor longitudinal changes in dietary intake throughout the study.
3. To periodically assess current individual intake for monitoring nutritional adequacy in the intervention group.
4. To periodically assess individual and group adherence to dietary intervention objectives in the intervention group.

7.4.2 Methods

The proposed methodologies to meet these objectives include the following for both intervention and usual care group participants (Table 7-3):

1. Dietary Eligibility Questionnaire (modified from Connor and Connor) completed at first screening visit: (DISC I)
 - a. To determine eligibility based on current food selection patterns that will ensure adequate margin for change.
 - b. To assess capability and willingness to participate in the study.
 - c. To identify baseline eating patterns.
2. Multiple (3) 24-Hour Random Recalls completed by children at baseline, 12 months, 36 months, Year 5, Year 7, Year 9 and the final visit. One face-to-face and two telephone recalls will be administered within two weeks and will include one weekend day per record: (DISC I and II)
 - a. To establish baseline and follow-up visit individual and group dietary intakes for end point data analyses.
 - b. To assess weekday versus weekend eating patterns.
 - c. To assess dietary adequacy of intakes at baseline and follow-up visits.
 - d. To assess levels of participant/parental cooperation and adherence.
 - e. To provide preliminary evidence to the feasibility study of participant adherence to the diet.

Proposed methodologies to meet dietary assessment goals which will be used in the intervention group only include the following (Table 7-2):

1. Diet Patterns Questionnaire completed by parent/caretaker at baseline: (DISC I)
 - a. To assess child's behaviors that influence food intake such as meal and snacking patterns and eating outside the home.
 - b. To assess parent's/caretaker's behaviors that influence child's food intake such as food purchasing and preparation methods.
2. Three Day Food Records or Recalls completed by children at regular intervals throughout intervention: (DISC I and II)
 - a. To assess baseline eating patterns in individuals in intervention group.
 - b. To measure dietary adherence to recommended eating pattern during follow-up.
 - c. To assess dietary adequacy and nutrient intake during follow-up.
3. GO/WHOA Checklists between intervention visits: (DISC I and II)
 - a. To provide opportunity for self-assessment of dietary adherence.
 - b. To provide opportunity for self-assessment of dietary change over time.
4. DISC Intervention Goals completed by parent/caretaker and child during intervention visits: (DISC I and II)
 - a. To allow participants to specify in writing at each intervention session a behavioral goal.
 - b. To allow self-monitoring of achievement of goals.
5. Monthly Contact Form completed by clinic personnel listing nature of monthly contacts with intervention group parents and children. Returned to Coordinating Center monthly until July 1, 1993. (DISC I)

6. Growth Monitoring Form completed by clinic interventionists and recording intervention children's height and weight measured every three months beginning at 15 months and ending July 1, 1993. (DISC I)
7. Participant Tracking Form completed by clinic personnel every six months beginning July 1, 1993 until the final visit. Records monthly participant contacts and mid-year results of height and weight measures for intervention group participants. (DISC II)
8. Saturated Fat Monitoring Book developed by DISC as a specialized tool that will assist participants to identify and control sources of saturated fat in their diet. It was designed to act as an aid to self-monitoring and will be used on a case by case basis during individual visits with older intervention group participants. (DISC II)
9. Diet Acceptability Questionnaire (DAQ) administered to parents and children every 6 months in DISC I and to children yearly in DISC II to evaluate both general reactions and specific problems in carrying out the DISC diet.
10. Case Management Conference and Case Management Summary Form A case management conference will be held every six months in DISC I and yearly in DISC II. During the conference, clinic staff will focus on individual intervention participants and their families. Their purpose will be to exchange information, evaluate the adherence of each participant, and facilitate better adherence to the recommended diet. A Case Management Form will be completed for each participant at his/her conference and will record the information reviewed and decisions made. (DISC I and II)
11. Knowledge Test is a 20 question multiple-choice test of participant knowledge of the saturated fat content of various foods. It was

designed by DISC nutritionists as a tool to be used on a case by case basis during individual intervention sessions to assess participant knowledge of recommended food choices. (DISC II)

12. Confidence Rating Form I adapted from a section of the Barr Taylor Diet Self-Efficacy Scale (DSES)¹¹ developed at Leland Stanford Jr. University. This form asks participants to rate their confidence that they can control their eating habits. It will be administered to intervention and control group participants at the final visit. (DISC II)

13. Confidence Rating Form II adapted from a section of the Barr Taylor Diet Self-Efficacy Scale (DSES)¹¹ developed at Leland Stanford Jr. University. This form will be administered to intervention group participants only beginning at IY06 and asks participants to rate their confidence that they can stick to a low-fat eating pattern. (DISC II)

14. The DISC Cookbook is a collection of recommended and tested recipes provided by DISC intervention group participants. The Cookbook will be distributed at all DISC clinics at intervention sessions. Children will receive credit for their contributions. (DISC II)

15. The DISC Dictionary is a dictionary of recommended foods, advice on preparation, serving and portion sizes, and nutritional content by food group. (DISC I and II)

16. The Food Record Guide is supplied to intervention group participants to use as an aid in measuring and reporting food intakes on food records and recalls. The goals are to improve accuracy of the records and recalls. (DISC I and II)

7.4.3 Rationale

Only children whose dietary fat intake at the first screening visit is sufficient to allow a margin for intervention will be eligible to participate in DISC. The Diet Eligibility Questionnaire will assess usual fat intake and will be designed so that it can be easily administered and scored at clinical centers.

Dietary data used to assess efficacy and safety of the intervention in the feasibility and full-scale trials will be derived from three 24-hour recalls collected from the intervention and control groups at baseline, 12 and 36 months, Year 5, Year 7, Year 9 and at the final visit, plus one 24-hour recall at 6 months for the feasibility group only. Multiple recalls will be used because of the large intra-individual variation in daily dietary intake. The first of the three recalls will be performed in-person and the second two will be performed over the telephone. The in-person recall will provide the opportunity for familiarizing participants with the method and instructing them on using two dimensional food models. The telephone recalls will provide the opportunity for collecting dietary data on random days. Therefore, participants will not be able to vary their intakes on particular days because they know they will be asked what they ate. Also, telephone recalls will decrease the number of clinic visits participants have to make and possibly reduce contamination of controls.

Ongoing evaluation of adherence and nutritional adequacy in the intervention group will be performed using 3-day food records or recalls. Food records or recalls will be completed at regular intervals throughout intervention, using the method that nutritionists and children feel most comfortable with.

In addition to providing a means for monitoring adherence and safety, 3-day food records will be used by dietitians at clinical centers as a teaching tool. Nutrient intake will be evaluated by dietitians using a

micro-computer based nutrient analysis system (NDS). This will provide rapid feedback of information to participants and maximize usefulness of the data. The DISC GO/WHOA Checklist, Diet Patterns Questionnaire, and Intervention Goals, the Saturated Fat Monitoring Book, The Knowledge Test, the DISC Cookbook, the Dictionary, and the Food Record Guide are intervention tools that are intended to enhance adherence to the DISC diet.

7.4.4 Nutritional Coding and Analyses

The 3-day food records and 24-hour recalls will be coded using the Nutrition Coordinating Center (NCC) data base. Over 60 nutrients are included and together provide detailed information regarding dietary intake.

DISC dietary recommendations are primarily focused on fatty acids and cholesterol. Meeting adequacy requirements for other nutrients focuses on percent of calories from protein, vitamins A and C, iron, zinc, and calcium relative to the usual care group and RDA recommendations.

Assessment of dietary adherence will be based upon the variables that best reflect the change from a high fat intake at baseline to a lower fat intake following intervention. The assessment of adherence to dietary recommendations in DISC will include the following factors in terms of both grams and percent of total calories: total fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PFA), monounsaturated fatty acids, and cholesterol. Dietary adherence will also be assessed by means of the Keys Score, defined as

$$1.35[2(\%SFA \text{ kcal})-(\%PFA \text{ kcal})] + 1.5(\text{mg cholesterol}/1000 \text{ kcal})^{1/2}.$$

The intervention group means will be compared as well as the percent of the DISC goals achieved and the percent of participants who achieve them. The Keys Score, although limited to fat and cholesterol criteria only, will also be calculated to reflect a change in these variables. Since the Keys

Score predicts the potential serum cholesterol lowering effect of reduced fat intake, the lower the Keys Score the better the response.

It is helpful to study multiple nutrients and dietary factors to provide a general picture of the initial compliance with dietary intervention. Among these factors the Keys Score serves as a valuable measure of dietary adherence since it incorporates the weighted effects of three factors known to influence blood cholesterol simultaneously. The Keys Score is not intended to predict cholesterol response in this case, but only to serve as one of the measures of dietary adherence.

7.5 Physical Activity Assessment

7.5.1 Objectives

The primary objectives for assessing physical activity in DISC are:

1. To estimate baseline level of activity in study participants and monitor change over time.
2. To rank participants according to activity level (e.g., high, medium, low) so that potential confounding of the association between diet and blood lipids or hormone levels and blood lipids by physical activity can be evaluated and, if appropriate, adjusted for in analyses.
3. To identify intervention group participants who are either very active or very sedentary to help explain possible differences in lipoprotein response.

7.5.2 Methods

There are currently no satisfactory standards for adequately measuring physical activity in children. Various assessment tools have been used in previous studies and these have been reviewed for applicability to DISC. The DISC Physical Activity Questionnaire was adapted for children from physical activity recall items developed for adults at Stanford University.¹²

Physical activity will be assessed using the interviewer-administered DISC questionnaire completed by the parent with input from the child in DISC I and by the child with help from the parent in DISC II. The questionnaire will be administered at baseline, 12 and 36 months, Year 5, Year 7, Year 9 and at the final visit.

7.6 Makeup of a Clinic Visit and Time Table

Children in both the control and intervention groups will be seen at two screening visits, a baseline visit, at 6 months (feasibility study only) and then annually following randomization. Data to be collected at clinic visits will include history, dietary assessment, physical examination including anthropometric data, serum lipid and lipoprotein levels, other laboratory tests for exclusion and monitoring, and psychometric tests. The administration schedule is outlined in Tables 7-4 and 7-5. Table 7-6 summarizes the schedule of administration of selected intervention forms for intervention group children and their parents.

7.7 Priorities for Data Collection

Priorities for data collection for all in-clinic visits will be the same as for non-clinic visits (See Chapter 20 in the DISC Manual of Operations "Procedures for Non-Clinic Data Collection Visits in DISC"). The measurement of height and weight and obtaining blood for lipids are the highest priority items. The priority ranking for annual visit data collection is as follows: HIGHEST PRIORITY:

1. Height
2. Weight
3. Blood draw (when required for visit)

SECONDARY PRIORITY:

4. Menses data (when required for visit)

5. Medical history and tobacco use
6. 24-hour dietary recalls (when required for visit)
7. Physical activity assessment (when required for visit)
8. Maturation assessment
9. Complete anthropometry (when required for visit)
10. Blood pressure (when required for visit)
11. Psychosocial assessments (when required for visit)

Data should be obtained on the highest priority items, and as much of the data as possible on the secondary priority items. If the participant refuses to provide the information or to allow examination, data collection should proceed on to the next item.

7.8 References

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Table 7-1

Table 7-1							
A. Psychosocial Assessment Instruments Used To Monitor Dietary Safety. (Control and Intervention Groups in DISC I and II)							
<u>Variable and Measure</u>	<u>Time for Admin.</u>	SV2	BL	IV1*	<u>Visit</u> 12 Mo.	36 Mo.	Final
1. Cognitive Development							
. Woodcock-Johnson Math/Reading	25 min.		C		C	C	C
2. Behavior Problems							
. CBCL	20 min.	P		P	P	P	P
. Youth Self Report	20 min.						C
3. Self-Reported Emotions and Attitudes							
. Child Depression Inventory	10 min.		C		C	C	
. Beck Depression Inventory	10 min.						C
. Trait Anxiety Inventory (child version)	10 min.		C		C	C	
. Trait Anxiety Inventory (adult version)	10 min.						C
4. Family Environment Scale	25 min.		P		P	P	P
B. Psychosocial Assessment Instruments Used to Predict Dietary Compliance (Intervention Group Only in DISC I).							
<u>Variable and Measure</u>	<u>Time for Admin.</u>	SV2	BL	IV1*	<u>Visit</u> 12 Mo.	36 Mo.	Final
1. Compliance with Instructions							
Child Behavior Inventory	10 min.			P			
2. Recent Stressful Events							
Life Experience Scale	20 min.			P			
3. Social and Economic Resources							
Demographics--Education, Occupation, Income, Household Composition, Race	10 min.	P					
P = Parent C = Child * First intervention visit							

Table 7-2

Total Amount of Time Required to Administer DISC Psychosocial Assessment Instruments to Parent and Child at Baseline (BL), 12 Months, 36 Months, and Final Visits.

<u>Participant</u>	<u>Visit</u>					
	<u>SV2</u>	<u>BL</u>	<u>IV1*</u>	<u>12 Mo.</u>	<u>36 Mo.</u>	<u>Final</u>
Parent	30 min.	25 min.	30 min.	45 min.	45 min.	45 min.
Child		45 min.		45 min.	45 min.	65 min.

*First intervention visit.

Table 7-3

DIETARY ASSESSMENT METHODS AND TOOLS FOR DISC

Method	Objective	Target Variables	Frequency of Administration
I. Intervention and Usual Care Groups:			
Dietary Eligibility Questionnaire	# Quick estimate of usual individual intake for eligibility # Assess willingness to cooperate with dietary intervention	# Intake of high fat foods	Screening Visit 1 (DISC I)
3 X 24 Hour Recalls (1 at clinic, 2 telephone)	# Assess mean intake of individuals # Assess nutritional adequacy # Assess adherence # Assess changes in dietary intake	# Macro- and micro-nutrients and calories	Baseline, 12 months, 36 months, Year 5, Year 7, Year 9 and Final Visit (DISC I and II)
II. Intervention Group Only:			
3 Day Food Record	# Assess current mean intake of individuals # Measure dietary adherence # Assess changes over time	# Macro- and micro-nutrients and calories # Food groups	Regular intervals throughout intervention (DISC I and II)
GO/WHO A Checklist	# Assess habitual meal and snacking pattern # Scoring of weekly meal pattern for self monitoring	# Use of high fat and/or undesirable foods	Between intervention sessions (DISC I and II)
Diet Patterns Questionnaire	# Assess family resources # Assess child's & parents/caretakers behaviors that influence food intake	# Food preferences, purchasing and preparation, eating out	Parents at baseline (DISC I)
DISC Intervention Goals	# Assess weekly achievement of specified diet intervention goals	# Food selection, purchasing, preparation and modeling behavior	Parents and children at intervention visits (DISC I and II)

Table 7-3 (Continued)			
DIETARY ASSESSMENT METHODS AND TOOLS FOR DISC			
Method	Objective	Target Variables	Frequency of Administration
Monthly Contact Form	# Assess nature of monthly contact	# Attendance and participation in intervention sessions	Monthly by clinic personnel (DISC I)
Participant Tracking Form	# Assess nature of contacts within 6 mon. tracking period	# Attendance at intervention sessions, mail and phone contacts	Every 6 mons. by clinic personnel (DISC II)
Growth Monitoring Form	# Monitor height and weight between data collection visits	# Child Growth	Every 3 months from 15 months to 7/31/93 (DISC I)
Case Management Form	# Record results of case conference	# Adherence to diet; monitor height, weight, adequacy of dietary intake	Every 6 months (DISC I); every year (DISC II)
Diet Acceptability Questionnaires	# Evaluate general reactions to diet and specific problems	# Diet acceptability	Parents and children every 6 mons (DISC I) and children yearly (DISC II)
Confidence Rating Form I	# Evaluate feelings of control over eating habits	# Diet Self-Efficacy	One time at the final visit (DISC II)
Confidence Rating Form II	# Evaluate ability to stick to a low-fat eating pattern	# Diet Self-Efficacy	Annually after IY06 (DISC II)
Saturated Fat Monitoring Book	# Reduction of saturated fat intake through self-monitoring	# Dietary intake of saturated fat	Throughout intervention on an individual basis (DISC II)

Table 7-3 (Continued)

DIETARY ASSESSMENT METHODS AND TOOLS FOR DISC

Method	Objective	Target Variables	Frequency of Administration
Knowledge Test	# Improved dietary choices of foods low in saturated fat	# Knowledge of the DISC recommended diet	Throughout intervention on an individual basis (DISC II)
DISC Cookbook	# Cooking practice; better use of low fat recipes at home	# Preparation of low fat recipes	Throughout intervention (DISC II)
DISC Dictionary	# Description of recommended foods, servings, and preparation by food group	# Knowledge of DISC diet and preparation by food group	Throughout intervention (DISC I and II)
DISC Food Record Guide	# Teach accurate estimation of food types and portions	# Reporting of intakes on food records and recalls	Throughout intervention (DISC I and II)

Table 7-4
Schedule of Information to be Collected in DISC I

Item	SV1	SV2	BV	<u>Months after Randomization</u>				
				6	12	24	36	48
Consent form								
Screening	A							
Baseline			A					
Demographic information	A							
Medical history								
Eligibility assessments	C	C,A						
Family history		A						
Illness, medications	C,A			C			C	C
Physical examination								
Height, weight		C	A	C	C	C	C,A	C
Blood pressure		C	C		C		C,A	C
Skinfold thickness								
Triceps		C			C		C	
Subscapular, suprailiac		C			C		C	
Arm, waist, hip circumference		C			C		C	
Tanner staging		C		C	C	C	C	C
General physical exam		C			C		C	
Menses calendars							C	
Dietary assessment								
Dietary Eligibility Questionnaire	C			C				
3 24-hour dietary recalls			C	C*	C		C	
Physical activity assessment			C		C		C	
Psychosocial assessment								
Woodcock-Johnson			C		C		C	
Achenbach CBCL		A			A		A	
Child Depression Inventory			C		C		C	
State-Trait Anxiety Inventory			C		C		C	
Family Environment Scale			A		A		A	
Biochemical determination								
TC, TG, HDL-C, LDL-C, apo A-I, apo B	C	C	A**	C**	C		C#,A	C
Albumin		C			C		C	
SGPT, glucose, chemistry panel		C					C	
Urinary protein		C**						
T4		C						
Hemoglobin, hematocrit, ferritin, zinc, copper, retinol, tocopherol, carotenoids, folate		C			C		C	
Linoleate:oleate ratio		C		C				
Hormone assaysH					C		C	

C = Child

A = Adult

*A single 24-hour dietary recall at 6 months, feasibility group only

**Feasibility study only

#Two determinations one month apart

HEstrone, steroids, bioavailable fractions, and SHBG

Table 7-5

SUMMARY OF DISC II CLINIC VISIT CONTENT
(Children Only)
August 1993 - January 2001

Months After Randomization/ Visit Number	36* MN36	48 MN48	60 YR05	72 YR06	84 YR07	96 YR08	108 YR09	Final# FV01	Final Repeat FV02
MEDICAL HIST.: Illness, Hospit., Meds, Pregnancy	X	X	X	X	X	X	X	X	X
PHYSICAL EXAM:									
Height, Weight	X	X	X	X	X	X	X	X	
Blood Pressure	X							X	
Skinfolds	X							X	
Circumferences	X							X	
Tanner Stage**	X	X	X	X	X	X	X	X	
Menses Calendars	X		X		X		X	X	X
Gen. Physical	X							X	
DIETARY ASSESS.: 3 - 24hr.recalls	X		X		X		X	X	
PHYSICAL ACTIV. ASSESSMENT	X		X		X		X	X	
PSYCHOL.BATTERY	X							X	
BIOCHEMICAL TESTS:									
Lipids, Apos	X		X		X		X	X	X
Chemistry Panel&	X							X	
CDC Assays***	X							X	
Hormone AssaysH	X		X		X		X	X	X

DNA ANALYSES[@]

*DISC I only

#Randomization anniversary after 18th birthday

**Until Tanner stage 5 only

&Serum albumin, SGPT, fasting serum glucose, serum urea nitrogen, creatinine, total and direct bilirubin, calcium, phosphorus, uric acid, total protein, SGOT, and alkaline phosphatase.

***Ferritin, Zinc, Copper, Retinol, Tocopherol, Carotinoids, Red Cell Folate
HEstrone, steroids, bioavailable fractions, and SHGB

@DNA polymorphisms in the APOA-I promoter, the APOE, and APOA-IV genes. One-time collection after YR06.

Table 7-6

SCHEDULE FOR THE ADMINISTRATION OF DISC I AND II
Intervention Forms

			FORM				
	Diet Eligibility:	Diet Patterns:	Diet Acceptability (DAQ)				Case Management Summary
	Form 21	Form 24	Form 17: Baseline	Form 18: Interim	Form 52: Annual	Form 49: Annual	Form 58
VISIT							
SV1	C						
BL		A	C				
5 weeks				C		A	
12 weeks				C		A	
6 months*				C		A	
12 months*					C	A	
24 months					C	A	
36 months*					C	A	
42 months							C
48 months*					C	A	
54 months							C
60 months*					C		
66 months							C
72 months*					C		
78 months							C
84 months*					C		
90 months							C
96 months*					C		
102 months							C
108 months*					C		
Final*					C		C

C = child A = adult

* studywide data collection visits/ \pm one month window

05/23/95

CHAPTER 8

INTERVENTION

8.1 Dietary Goals and Rationale8.1.1 Target Nutrient Composition

The DISC Diet will be a balanced diet that is restricted in fat, particularly saturated fat. Dietary goals for DISC are as follows:

	<u>% Calories</u>
Protein	14 2/3 animal, 1/3 vegetable
Fat	28
SFA	8
PUFA	9
MUFA	11
Carbohydrate	58

Encourage water soluble fiber

Cholesterol < 75 mg/1000 calories (Not to exceed 150 mg/day in DISC I, with no daily limitation in DISC II.)

Meet the Recommended Dietary Allowances (RDA) for all nutrients.

8.1.2 Comparison to U.S. Diet

Data from the NHANES II on dietary intake of U.S. children 9-11 years old indicate that children consume approximately 37.4% of calories from fat and 14.6% from protein with the remainder coming from carbohydrates. Saturated fatty acids (SFA) make up approximately 13.2% of calories and polyunsaturated fatty acids (PUFA) make up 4.9% of calories yielding a P/S ratio of 0.4. Children consume approximately 276 mg of cholesterol per day or 136 mg per 1000 kcal.

The dietary prescription for DISC will reduce total fat intake to 28% of calories and increase the P/S ratio to approximately 1.1. This

will be accomplished by reducing intake of SFA to less than 8% of calories and decreasing MUFA to 11% while increasing PUFA to 9% of calories. Cholesterol will be restricted to less than 75 mg/1000 Kcal, not to exceed 150 mg/day. In DISC II the 150 mg/day limitation on dietary cholesterol was dropped to accommodate the higher caloric intakes of older children and adolescents. The protein content of the diet will be unchanged essentially, i.e., 14% of calories will be derived from protein with one-third of the protein calories coming from vegetable sources. The diet will be designed to meet energy needs. (See Section 8.4 on weight for height.) The remaining 58% of calories will come from carbohydrates. Water soluble fiber will be encouraged to enhance cholesterol lowering.

8.1.3 Progression

The DISC diet will be introduced in its entirety at the beginning of the intervention. It is likely that the children may take six months to achieve the nutrient intakes specified by the DISC diet.

8.1.4 Efficacy

Based on Keys' formula,¹ the proposed diet will reduce serum total cholesterol by 25.5 mg/dl if the baseline serum cholesterol level of the children is 212 mg/dl. Corrected for lower average serum cholesterol levels of 185.8 mg/dl in children in the 75th - 98th percentile for cholesterol, the expected drop in serum cholesterol in the intervention group is 10.6% to 166.1 mg/dl. Data from the other studies² suggest that the magnitude of the decrease in LDL-C will be at least equal to the decrease in total cholesterol. Therefore, a larger relative decrease in LDL-C is anticipated. Increased consumption of water soluble fiber may further decrease serum cholesterol levels.

8.1.5 Adequacy

The DISC diet will provide the RDA for all nutrients. Based on data from Bogalusa, 60% or more of ten year old children consume less than 67% of the RDA for vitamins D, B₆ and folacin. Almost 40% of children consume less than 67% of the RDA for vitamin C and zinc. These nutrients and iron and calcium will receive special attention in the DISC diet. Because fat in the diet is targeted at 28% of calories, particular attention will be given to meeting energy needs.

8.1.6 General Food Pattern

The DISC diet is lower in total fat, predominantly SFA, and higher in PUFA than the current diet of U.S. children. Beef, pork and mixed meat accounted for 28% of SFA in the diets of ten year old children in Bogalusa. Milk provided another 28% and desserts, candy, and breads provided 20%. Cholesterol was provided by similar sources except that eggs contributed 23%. Restriction of SFA and cholesterol in DISC will result from significant decreases in fatty meats, whole milk, commercial baked products, candy and egg yolk. Lunch, dinner and snacks will equally contribute more than 80% of SFA and cholesterol intake. Each of these eating periods will be designed to achieve adherence to the DISC dietary goals.

8.2 Intervention Approach

8.2.1 General Approach

Intervention in DISC will be provided through group sessions and individual family sessions. An intense intervention phase of about 12 months duration will be followed by long-term intervention and then a period of maintenance. The intense phase of the intervention will include 15 group sessions and five individual family sessions. Initially, intervention sessions will be held weekly. After the first

six sessions, participants will meet biweekly. Long-term intervention and maintenance will consist of regular sessions, at least two group and two individual sessions per year in DISC I, at least two face-to-face sessions per year in DISC II until about Year 06, and at least three face to face sessions using the "personalized contact" method after Year 05 (see section 8.3 for details). Other intervention contacts will be arranged as needed. At least once per month families will be contacted by phone or mail.

8.2.2 Group Sessions

Most of the DISC intervention will take place during group sessions led by nutritionists and behaviorists. Groups will be made up of approximately ten families. Group sessions will be 100 minutes in duration. First, children and parents will meet jointly for a brief five minute overview and then separately for a 35 minute session. These separate groups will emphasize food information and skills, motivation for behavior change, support for behavior change and food preparation. They will then have a meal as a family with DISC diet appropriate foods (25 minutes). The joint family group will then discuss family support for change and past and future goals (40 minutes). DISC intervention will take a food group approach to diet modification. The majority of group sessions will target a particular food group. Within that food group desirable ("GO") foods will be identified and encouraged and undesirable ("WHOA") foods will be identified and discouraged. There will be additional group sessions on shopping and label reading, fast foods and recipe modification. The content of children's group sessions will parallel the content of adults' group sessions.

A number of behavior change techniques will be used in group sessions. Information will be provided verbally and in writing. Activities including demonstrations, games and food tasting will be used to reinforce didactic material and encourage dietary change. Goal setting and problem solving will be utilized to produce compliance with DISC dietary goals.

8.2.3 Individual Sessions

Individual family sessions will be held in conjunction with group sessions during intervention. These family sessions will usually occur either before or after the group session. They will be designed to discuss and resolve individual family issues and other problems that are not being dealt with effectively in group sessions. They will also be used to make up missed material when a participant is absent from a group session. The individual session will be with a nutritionist or behaviorist depending on the specific needs of the participant.

8.3 The Personalized Contact Method and Case Management

8.3.1 Overview

The goal of intervention after Year 05 is to personalize dietary guidance among older adolescents and to maximize adherence according to each individual's current status. This process begins with reassessment of both usual dietary intake and readiness to change. Together, the interventionist and participant will establish new goals for achieving dietary adherence and target solutions to relevant problem behaviors.

DISC I established the cognitive foundation for the recommended diet and explained how saturated fat and cholesterol contribute to blood cholesterol. Much of this was achieved through group process in a family setting with individual follow-up to reinforce these universal

goals at an individualized level. DISC II added to that foundation the concepts of Social Action Theory³ to identify the individual's priorities and attempt to mesh them with the study goals. After Year 05, DISC will further build upon this knowledge base and attempt to motivate each participant individually to accept accountability for making desirable behavior changes. This represents a decisive shift away from family and parentally oriented methods to self-directed participant intervention and self-rewards.

During DISC I-II, maintenance of adequate fat intake at around 28% of total calories was encouraged to prevent growth failure. After Year 05, DISC dietary intervention will be more aggressive. Participants who are currently adhering to the goal and are not at nutritional risk will be offered the opportunity to reduce total fat and thereby meet or further reduce the goal for saturated fat intake. The overall study goal will remain the same, but the individual goals will be based on current level of adherence and participants' expressed willingness to intensify adherence. Ongoing dietary assessment using NDS will ensure nutrient adequacy as well as dietary adherence to the reduced fat goals.

To summarize, the DISC intervention strategy after Year 05 will:

XShift the focus from group to individual interaction, using group activities as reinforcement.

XInitiate a case management approach that enlists participants as partners in establishing and monitoring new goals.

XRenew efforts to use motivational interviewing strategies.

Group efforts that were a successful feature of DISC I and DISC II will continue to be offered periodically. After Year 05, DISC will be geared to meet the needs of older adolescents who are more independent and have developed their own sets of priorities, separate and sometimes

conflicting with those of their parents and families. Knowledge of the diet will no longer be the limiting factor, rather, promoting the willingness of the adolescent to apply the appropriate eating behavior across a wide range of social settings will be the challenge.

8.3.2. Motivational Interviewing

DISC Interventionists will counsel each participant individually and address his/her willingness to change eating patterns that deviate from the recommended DISC diet. The "Stages of Change" model developed by Prochaska⁴ for adults will be adapted to this younger age group.

The stages include:

Stages of Change

1. Pre-contemplation
2. Contemplation
3. Preparation
4. Action
5. Maintenance
6. Relapse

Each participant's current stage of change will be assessed and further intervention will be initiated as warranted. For some participants, who are engaged in the action or maintenance stage, this will mean only continued support and encouragement. For others, who may have relapsed or never internalized responsibility for adhering to the diet without parental support, a more intensive effort will be needed.

DISC interventionists will assess the participant's current stage of change and seek ways to progress with each individual toward the goal of initiating action and maintenance of these changes.

The Motivational Interviewing method described by Miller and Rollnick⁵ will be applied to this process of assessing current stage of change and eliciting participant-initiated goals and objectives for the immediate future. The five fundamental principles are as follows:

Motivational Interviewing

1. Express empathy
2. Develop discrepancy
3. Avoid argumentation
4. Roll with resistance
5. Support self-efficacy

These principles support the interviewing method to be used in DISC after Year 05. In addition, the following elements described by Miller and Sanchez⁶, known as the FRAMES model will be incorporated as a personalized counseling tool. FRAMES will provide the steps used by interventionists in eliciting a self-directed action plan from the participant.

The letters of this acronym represent the following:

Feedback: Providing results to the participant on personal progress.

Responsibility: Establishing that it is the participant's choice to change.

Advice: Providing a prescription to assist in making a change.

Menu: Providing options for the participant to choose.

Empathy: Providing a supportive, caring environment in which the participant can make the changes.

Self-Efficacy: Reassuring the participant that he/she is capable of making the changes.

A detailed discussion of implementation methods and materials is presented in the DISC Manual of Operations Chapter 15, Section 15.2.

8.3.3 Visit Schedule

A minimum of three individualized contacts with each intervention group participant will take place annually. An annual case management staff conference will be held for all intervention participants. During the conference dietary adherence, related participant behavior, and remedial actions taken or planned will be discussed. A case management form and two follow-up visit forms detailing the results of

the initial case conference and the success of remedial actions taken will be completed annually and returned to the Coordinating Center.

8.4 Training and Certification

8.4.1 Training

Training for DISC interventionists will be provided through an Intervention Manual and skills training workshops. The Intervention Manual will be designed as a workbook including modules on interviewing, individual counseling, group counseling and case management. The material will be self-taught. Each module will include a pre-test and post-test for the interventionist to use to judge his/her mastery of the information.

Master trainers will be designated at each Clinical Center to train local personnel. A 4-day skills training workshop for trainers from all Clinical Centers will be held prior to the beginning of intervention. This workshop will provide practical experience in interviewing, counseling and leading groups. Additionally, participants will practice using intervention materials that will be used during the trial. Training materials as well as experience in training will be provided to participants. Interventionists certified as local master trainers will train other interventionists at their centers. Depending on needs, local workshops or individual training will be used.

8.4.2 Certification

Certification as an interventionist in DISC will require demonstration of knowledge of material included in the Intervention Manual. Additionally, the interventionist must participate in a skills training workshop or be trained by a designated master trainer and demonstrate that he/she has mastered the skills needed for effective

intervention. To be certified as an intervention master trainer, an interventionist must have satisfied criteria detailed in Section 15.9 of the DISC Manual of Operations.

8.4.3 Recertification

Yearly re-certification will be required for all previously certified nutritionists who are collecting data. For those who have not collected dietary data within the past nine months, re-certification will also be required. The re-certification process will be completed before each annual visit cycle.

The steps for local re-certification are detailed in the DISC Manual of Operations Section 15.10.1. No re-certification is required for master nutrition trainers.

8.5 References

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DISC Protocol
6/15/95

CHAPTER 9

CLINICAL MONITORING

CHAPTER 9

DIETARY INTERVENTION STUDY IN Participants (DISC)

CLINICAL MONITORING PROTOCOL

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CLINICAL MONITORING

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CHAPTER 9

DISC CLINICAL MONITORING

PREFACE

The Clinical Monitoring Committee has reviewed the clinical information that is available on the DISC participants. These data include anthropometrics, pubertal assessment, menstrual history, blood pressure, laboratory measures and psychosocial measures. The overall objective of this protocol is to notify the participant's medical caretaker of abnormal values that might require further evaluation and management.

Cutpoints for referral were selected that had reasonable sensitivity to detect various abnormal clinical conditions. The committee was concerned about over-referral as well as under-referral.

Where possible, the proportion of participants who would require follow-up utilizing the selected cutpoint was examined. A cutpoint was considered to be reasonable if the proportion of participants identified was reasonable (3-5%). Most of the participants identified for further evaluation on the basis of abnormal test values in a healthy asymptomatic population will be normal.

Evaluation and follow-up in the DISC center is proposed only for dietary problems in the Intervention group. For other abnormalities the parents of the participant will be given a DISC Referral Report with the relevant information for further evaluation and follow-up by the participant's private physician. The DISC centers do not have the capability to follow-up the abnormal values detected, including repeating laboratory tests, and are not the appropriate sites for further diagnostic or therapeutic care. A form to track follow-up of the identified participants will be used. The same cutpoints for %

ideal body weight as in the original DISC Growth Monitoring Protocol will be utilized but the height monitoring protocol has been modified and criteria for assessment of delayed puberty, low hemoglobin, low ferritin, high blood pressure, abnormal chemistries, abnormal lipids and eating disorders have been developed.

CHAPTER 9

DISC CLINICAL MONITORING

A. INTRODUCTION

This DISC Clinical Monitoring Protocol establishes the policy for monitoring of growth, nutritional adequacy, sexual maturation, blood pressure, blood chemistry and psychosocial development of DISC participants.

DISC has a responsibility to monitor the safety of the study in the Usual Care and Intervention participants and to assure the dietary safety of the Intervention participants. DISC monitors the effects of the dietary intervention in the Intervention participants by collecting and monitoring their height and weight and by performing periodic 24-hour dietary recalls (self-report by participants). In addition, blood pressure is measured and blood specimens taken from the study participants on a regular basis, and an assessment of Tanner stage is made. The DISC clinical monitoring is for screening purposes only (i.e. identification of possible medical problems requiring further assessment and possible referral), and is not intended to be diagnostic.

The purpose of clinical monitoring in DISC is to:

- 1) Detect and refer for assessment possible cases of inadequate growth or nutrition, delayed sexual maturation, blood chemistry abnormalities, or psychosocial abnormalities in the DISC study population.
- 2) Keep records of study participants identified as having potential problems and track their referral and follow-up.

This Clinical Monitoring Protocol will be used to provide guidelines for the assessment and the follow-up of any of the study participants who have been identified as experiencing possible problems in the areas listed above. If a participant exhibits signs of inadequate development, deficiencies or pathology in any of the defined areas, a Clinical Monitoring Form and clinical review will be initiated and, if necessary, a referral will be made. The mode of referral will be at the discretion of the DISC physician. The definitive assessment of the study participant's medical status will be carried out by his or her physician who will also be responsible for any treatment.

Mechanisms will be established to make sure that the DISC Coordinating Center is informed if a study participant is followed-up or re-examined according to the guidelines in this protocol, and the outcome of the assessment. The DISC Coordinating Center will maintain an updated database of possible and confirmed cases of medical problems in the DISC study population.

At the time of the writing of this protocol, a number of participants will have completed visits at which monitored assessments will have been made. The Clinical Centers and the Coordinating Center will use the most recent value for clinical monitoring purposes.

B. THE MONITORING SYSTEM

B.1 Introduction

A system will be established where an abnormal measurement, test, report or score which might indicate inadequate growth or nutrition, delayed sexual maturation, blood chemistry abnormalities, hypertension, or psychosocial abnormalities will be tracked. The following clinical indicators will be monitored:

- 1) For inadequate growth: weight, height velocity.

- 2) For anemia: hemoglobin, serum ferritin.
- 3) For delayed sexual maturation: Tanner staging of breast development and genital development, and age at menarche.
- 4) For excessive menstrual bleeding in girls at menarche: more than consecutive 10 days.
- 5) For hypertension: blood pressure.
- 6) For blood lipid abnormalities: lipid profile.
- 7) For blood chemistry abnormalities: identified tests from the blood chemistry panel.
- 8) For psychosocial abnormalities: psychosocial/developmental scores, eating disorders and reports of intended or attempted suicide.

The listed indicators are measured at the following visits.												
VISIT												
INDICATOR	BL	06	12	24	36	48	YR5	YR6	YR7	YR8	YR9	Final
Height	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin	X		X		X							X
Ferritin	X		X		X							X
Tanner Stage	X	X	X	X	X	X	X	X	X	X	X	X
Menstrual History					X		X		X		X	X
Blood Pressure	X		X		X							X
Blood Lipids	X		X		X		X		X		X	X
Blood Chemistry	X		X		X							
Psychosocial tests	X		X		X							X

B.2 Reporting Procedure

1. The DISC Coordinating Center will monitor the appropriate reports and test results. If a possible problem is identified among the study participants, a report will be sent to the Clinical Center where the study participant was seen. Follow-up based on the specific guidelines will be conducted at the Clinical Center, a Clinical Monitoring Form will be initiated and, if appropriate, a referral will be made. The mode of referral will be at the discretion of the DISC physician. The participant's private physician will make the final assessment of the condition. The local DISC Clinical Center will make all relevant information available to the participant's physician (e.g. dietary nutritional intake information).
2. If, in the process of examining a study participant, the DISC Clinical Center identifies a possible medical problem (e.g. low hemoglobin, high blood pressure), a Clinical Monitoring Form and review will be initiated. If appropriate, a referral will be made to the participant's private physician for further assessment, diagnosis and treatment without waiting for notification from the Coordinating Center. A copy of the Clinical Monitoring Form will be sent to the Coordinating Center.
3. All clinical monitoring values exceeding cutpoints should undergo clinical review at the DISC clinic in order to determine whether referral is needed. The clinical review can include retesting at the clinic's discretion. Results of the review should be documented on the Clinical Monitoring Form. For psychosocial results, the review should be conducted by the

clinic psychologist who will determine if referral is warranted. For medical results, the review should be conducted by the clinic physician. He/she will determine if the participant's medical values in conjunction with other risk factors warrant referral.

If the psychologist or physician determines that referral is not justified, the Clinical Monitoring Form question 2 should be completed by the clinic physician or psychologist with question 2D answered "No" indicating that a referral to an outside physician was not recommended. If he/she determines that a referral is justified, the Clinical Monitoring Form questions 2 and 3 should be completed and a referral made. The mode of referral will be at the discretion of the DISC physician or psychologist.

4. The Clinical Center should include a stamped, self-addressed envelope for the physician to return the Referral Report to the Clinical Center when completed. A copy of the completed Clinical Monitoring Form and Referral Report should be sent to the Coordinating Center by the Clinical Center. The participant's physician is responsible for any further follow-up and treatment of the participant. If the Referral Report has not been returned in three months, the parents or participant will be asked about the report and any visit to the participant's private physician.

B.3 Study Reports

The Coordinating Center will maintain the database for the clinical monitoring of the DISC study participants and will generate reports about the status of the ongoing clinical monitoring on a

quarterly basis for the DISC Clinical Monitoring Committee. Reports will also be prepared for review at meetings of the DISC Steering Committee and the DISC Data and Safety Monitoring Committee.

C. MONITORING FOR HEIGHT VELOCITY AND % IDEAL BODY WEIGHT

C.1 Introduction

If a Usual Care participant exhibits inadequate height velocity or becomes underweight, the participant will be referred to his or her physician as outlined below. If an Intervention participant exhibits inadequate height velocity or becomes underweight or overweight, this protocol will be used to investigate the situation and redirect the intervention as needed. Possible reasons for an intervention participant not growing or becoming underweight or overweight include misinterpretation of the diet (e.g., excessive fat and calorie restrictions) or a previously unrecognized medical condition.

The DISC Coordinating Center centrally monitors growth in height by keeping track of the participant's change in height since his or her last annual visit. In addition, the DISC Coordinating Center centrally monitors weight in relation to height and age by calculating the percent recommended body weight, or % ideal body weight (% IBW), for each participant using height, weight, age and gender. The % IBW will be determined for visits when height and weight measurements are collected (intervention visits and follow-up clinic visits). The information on height change and on % IBW is provided to the Clinical Centers for each participant and will be updated by the DISC Coordinating Center when height and weight are measured at an intervention or Clinical Center visit.

C.2 Height Velocity

Since inadequate nutrition may impair both pubertal development and height, height velocity as related to chronological age as recommended by Tanner is used. Cutpoints were selected based on Tanner's data of height velocity that presented the 3rd percentile of

height velocity for early, average and late maturers in boys and girls separately. Participants whose height velocity over one year OR over two years is less than the cutpoints will be identified as having a growth problem. Height Velocity Cutpoints:

	1 year	2 years
Boys (age 9 - 13)	< 3 cm	< 8 cm
Girls (age 8 - 11)	< 3 cm	< 8 cm

Height velocity falls rapidly after the age of 14 years in boys and 12 years in girls. Thus, after these ages, cutpoints to identify possible growth abnormalities were not established. Height velocity will not be monitored at the DISC II final visit.

A Clinical Monitoring Form and in-clinic review will be initiated for any participant identified as having a possible problem with height velocity. A referral will be made for any participant judged by reviewers to have a problem with height velocity. Further evaluation will be carried out by the participant's private physician.

C.3 Monitoring of % IBW

The following cutpoints and alert categories will be used to evaluate adequate % IBW among DISC participants.

A. Usual Care Participants

1. Alert % IBW:

Any Usual Care participant with less than 85.0% IBW will have a Clinical Monitoring Form and in-clinic review initiated. If necessary the participant will be referred for further evaluation by his or her private physician.

B. Intervention Participants (see Figure 5)

1. Acceptable % IBW (Between 90.0 - 130.0% IBW, inclusive):

For an Intervention participant who has an acceptable % IBW but whose dietary analysis indicates inadequate intake, initiate the following treatment plan:

Step 1. The nutritionist provides individualized dietary recommendations on how to increase whichever nutrient was less than 1/2 of the RDA assessed over three days (for calories, vitamin B6, vitamin A, or zinc), or less than 2/3 of the RDA assessed over three days (for protein, iron, calcium, or vitamin C). The participant will be re-evaluated in three months with a repeat nutritional assessment and repeat weight and height.

Step 2. For a participant who has an acceptable % IBW and who has received repeat dietary counseling to correct nutrient inadequacies for nutrients less than 1/2 RDA assessed over three days (calories, vitamin B6, vitamin A, zinc) or less than 2/3 RDA assessed over three days (protein, iron, calcium, vitamin C), no further intervention is required. Supplements are not recommended, although vitamin enriched foods such as Total cereal or calcium fortified orange juice can be recommended.

2. Worrisome % IBW:

Worrisome % IBW is defined in an Intervention participant with % IBW greater than or equal to 85.0 and less than 90.0% and a decrease of 12 or more percentage points away from 100% IBW in 12 months or less, or 8 or more points in 6 months or less.

For an Intervention participant who has a worrisome % IBW, a Clinical Monitoring Form and in-clinic review will be initiated and the participant will be re-evaluated within four weeks. Re-evaluation includes nutritional assessment, individualized nutrition counseling to correct inadequacies if present, and remeasurement of weight and height. If % IBW is still worrisome, a referral should be made.

3.Alert % IBW:

If an Intervention participant has a % IBW less than 85.0%, a Clinical Monitoring Form and review should be initiated and NDS dietary analysis should be repeated within four weeks. If NDS analyses indicate inadequate intake (as defined under Step 1 above), the participant should be counseled on the DISC Eating Plan within 2-4 weeks and the NDS and height and weight measurements repeated in 4-6 weeks. If the weight is not greater than 85% IBW and the NDS analysis indicates adequate intake, a Referral Report will be completed. The mode of referral is at the discretion of the DISC physician.

C.4 Weight Control (Intervention Participants only)

Any DISC Intervention participant or parent who requests assistance with weight control will receive evaluation and counseling from DISC intervention staff (see Figure 6).

1. Evaluation for Overweight or Excessive Increase in % IBW

First evaluate whether the Intervention participant is overweight under this protocol (greater than 130.0% IBW) or gaining excessive weight for height (increase in % IBW of 12 percentage points or more in 12 months or less, or 8 percent-

age points or more in 6 months). Investigate the possibility of measurement error. If there has been no weight or height recorded for the participant within the last two months, remeasure the participant's height and weight. If the participant still is greater than 130.0% IBW, or after examining several previous % IBW determinations and judging that there was excessive weight gain, discuss these findings at an individual visit with the family.

2. Discussion of Growth Data with Family

Review the growth data with the family at an individual visit.

3. Request for Assistance

If the participant or parent requests assistance with weight control, initiate a Clinical Monitoring Form and in-clinic review and implement the following intervention. A team approach involving a behaviorist, nutritionist, and the DISC family will be utilized.

The first step is to review the dietary data to determine whether the DISC diet is being followed. Re-emphasize following the DISC diet. Emphasize lowering fat intake as a method of achieving weight control. Develop a plan for self-monitoring that includes food choices, eating behaviors and portion control. Counsel on how to cut out, substitute for or cut down on high fat snack foods. Check for and encourage consumption of nonfat dairy products and counsel the participant to drink skim milk rather than 2% fat milk.

After this initial counseling, diet will be reviewed and the participant reweighed in four weeks. The aim is not weight

loss, but weight maintenance, or, during rapid linear growth, slowing of weight gain. If there is evidence of continuing excessive weight gain, the next step is to complete a Referral Report and refer the participant for further evaluation by his/her private physician.

Carefully document any weight reduction intervention implemented on the Clinical Monitoring Form so that these participants can be identified when DISC data are analyzed.

D.MONITORING OF PUBERTAL DEVELOPMENT

Failure to achieve these pubertal milestones at these chronologic ages will alert the Clinical Center to a possible abnormality in development. These milestones are based on the ages at which 95-97% of participants have achieved the particular stage of puberty, based on the data of Tanner. Any DISC participants who have not reached the indicated pubertal stage by the milestone age will have a Clinical Monitoring Form and in-clinic review initiated. If necessary, the participant will be referred for further evaluation by his or her private physician. These milestones for the initiation of puberty (Tanner II), for the progression to near completion of puberty (Tanner IV), and onset of menarche will be sufficient to detect disorders. Delay in pubertal maturation may indicate endocrinologic disorders, but may also indicate underlying chronic disease or poor nutrition.

Females

<u>Stage</u>	<u>Should reach stage by:</u>
Breast II	13 years
Breast IV	15.3 years
Pubic hair II	13.4 years
Pubic hair IV	15 years
Menarche	15 years

Males

<u>Stage</u>	<u>Should reach stage by:</u>
Testes 4 ml	13.5 years
Testes 12 ml	16.5 years
Pubic hair II	14 years
Pubic hair IV	16 years

E. MONITORING FOR EXCESSIVE MENSTRUAL BLEEDING

Most of the abnormal irregular bleeding patterns such as oligomenorrhea, polymenorrhea, menorrhagia or "intermenstrual" bleeding in the adolescents are indicative of anovulatory cycles. They are most commonly of short duration, are frequently prone to spontaneous corrections, and will require no particular intervention from the medical community.

However, in a few cases, dysfunctional menstrual bleeding patterns might indicate possible problems of the pituitary, thyroid, adrenal or ovarian function or other medical problems. Therefore, girls at menarche, who report excessive bleeding (more than 10 consecutive days) on their menstrual calendars, will have a Clinical Monitoring Form initiated and be flagged for review by the clinic physician. If necessary, a referral will be made to the participant's physician.

F. MONITORING FOR ANEMIA AND LOW FERRITIN

F.1 Introduction

This protocol will be used to monitor for anemia and low ferritin levels using hemoglobin and serum levels of ferritin.

F.2 Hemoglobin Monitoring

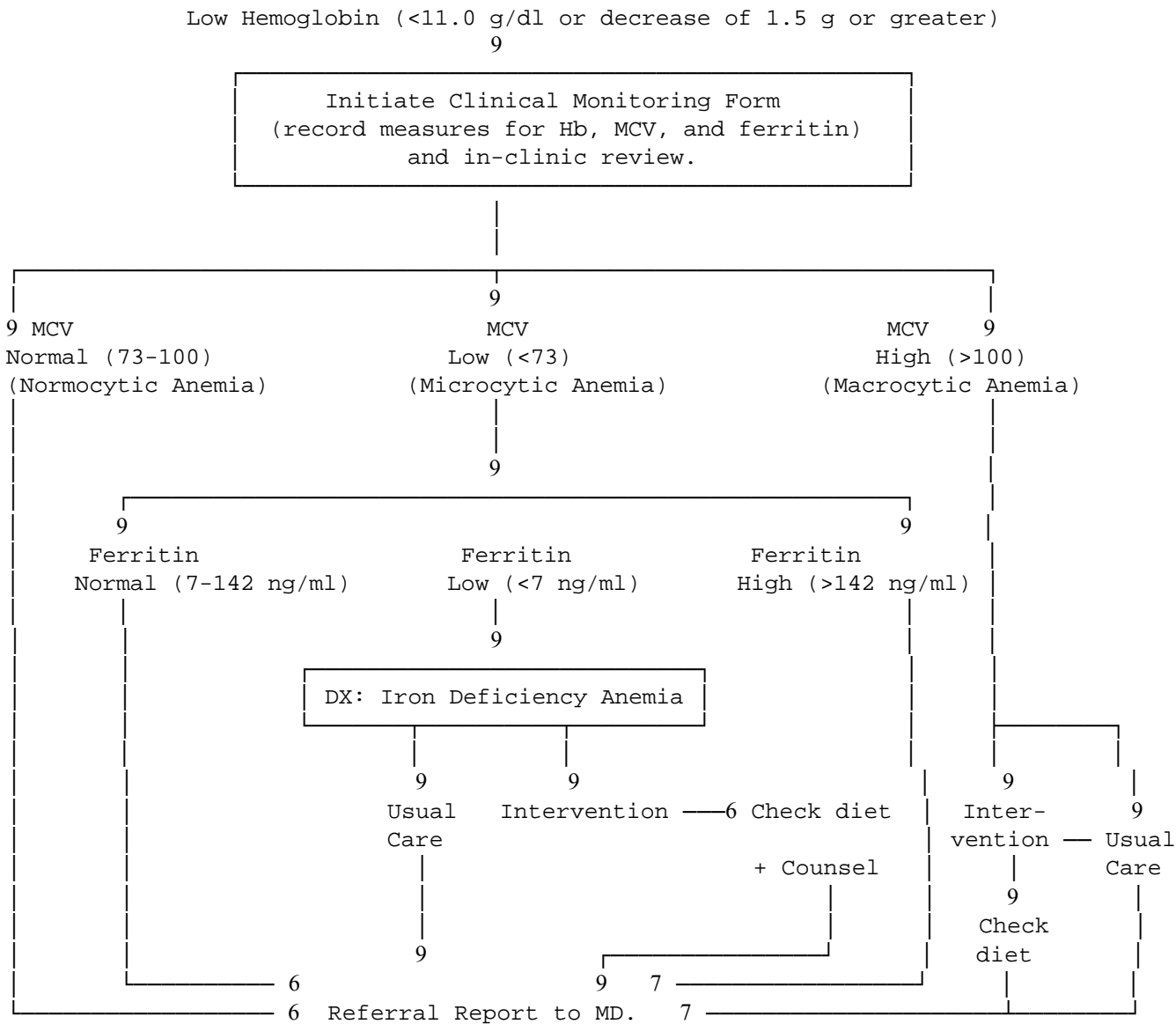
A hemoglobin less than 11.0 g/dl or a decrease of 1.5 g/dl or greater between measurements will be considered a "low" hemoglobin. Any participant with a low hemoglobin will have a Clinical Monitoring

Form and an in-clinic review initiated. If necessary, the participant will be referred for appropriate evaluation, treatment, and follow-up by his or her private physician. When a low hemoglobin is identified, the mean corpuscular volume (MCV) and serum ferritin already obtained will be reviewed. If the MCV is low (less than 73) and the ferritin is low (less than 7 ng/ml), the participant has iron deficiency anemia.

When a DISC Intervention participant is identified as having iron deficiency anemia, his/her diet will be reviewed by the DISC nutritionist and the participant and family counseled about iron rich foods. Iron supplements will not be recommended. Intervention participants identified with low hemoglobin and high MCV (greater than 100) will have their diets reviewed for the very unlikely possibility of folate or vitamin B12 deficiency. If a dietary deficiency is found, they will be counseled about foods rich in these nutrients. The information will be included in the Referral Report for further follow-up by the participant's private physician.

Usual Care participants with a low hemoglobin will have a Clinical Monitoring Form and review initiated. If necessary, they will be referred for further evaluation by their private physician.

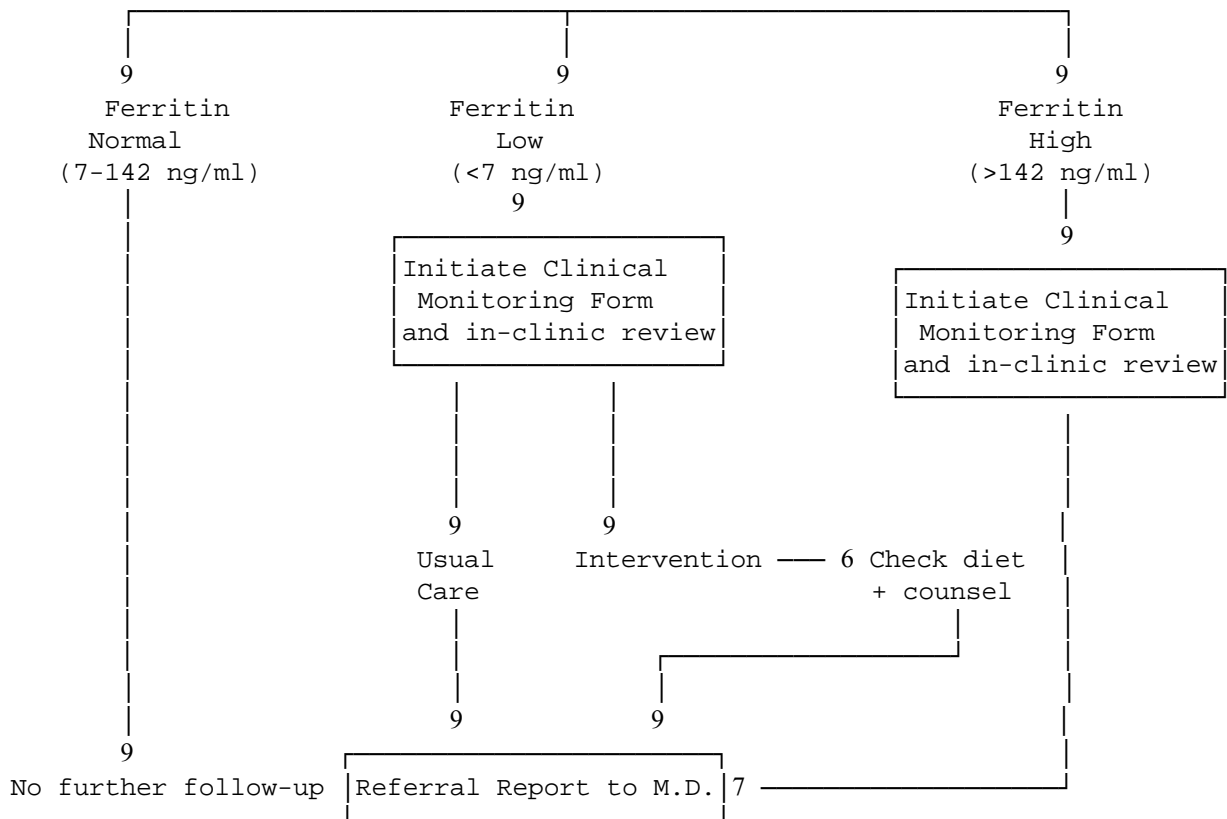
A diagram of this process is as follows:



F.3 Serum Ferritin Monitoring

A normal serum ferritin is 7-142 ng/ml. A low ferritin is less than 7 ng/ml. A DISC Intervention participant with a low serum ferritin will have his/her diet reviewed and, along with the parents, counseled regarding iron rich foods. Iron supplements will not be recommended. Participants with low serum ferritin will be reviewed, and, if necessary, referred to a pediatrician for follow-up. For

intervention participants, dietary information obtained should be included in the Referral Report. In the unlikely event a serum ferritin is elevated, a Clinical Monitoring Form and in-clinic review will be initiated. If reviewers determine that a referral is necessary, a Referral Report will be completed and the participant will be referred for evaluation by his/her private physician. A diagram of this process is as follows:



G. BLOOD CHEMISTRY MONITORING

G.1 Introduction

Blood chemistries will be monitored for potential undetected diseases or conditions.

G.2 Blood Chemistry Monitoring

Blood chemistries of DISC participants will be monitored for values outside the normal range using the following limits (calculated as the normal mean +/- 3.S.D. based on "Normal Range" from the Central Non-Lipid Laboratory at Johns Hopkins Hospital).

Blood Chemistry Monitoring Cutpoints

Variable	"Normal Range"	Lower Limit	Upper Limit
Albumin	3.5 - 5.3 g/dl	3.1	5.8
Total Protein	6.0 - 8.2 g/dl	5.5	8.8
SGPT (ALT)	0 - 54 IU/l	--	67.5
SGOT (AST)	20 - 65 IU/l	--	76.3
Glucose	60 - 100 mg/dl	50.0	110.0
Urea Nitrogen	7 - 22 mg/dl	--	25.8
Creatinine	0.5 - 1.0 mg/dl	--	1.1
Total Bilirubin	0.3 - 1.2 mg/dl	--	1.4
Direct Bilirubin	0.0 - 0.4 mg/dl	--	0.5
Calcium	8.0 - 10.5 mg/dl	7.4	11.1
Phosphorus	3.2 - 6.3 mg/dl	2.4	7.1
Uric Acid	2.0 - 5.5 mg/dl	1.1	6.4

Any participant with blood chemistry values less than the lower limit or greater than the upper limits will have a Clinical Monitoring Form and in-clinic review initiated. If necessary, they will be referred for further evaluation by their private physician. Blood

chemistries will not be collected or monitored at the DISC II final visit.

H. BLOOD LIPID MONITORING

Blood lipids will be monitored to identify participants whose values are outside acceptable levels. The referral cutpoint for triglycerides is that used during the screening process to exclude individuals and refer them for medical evaluation. Any participant with a triglyceride level outside the limit will have a Clinical Monitoring Form and in-clinic review initiated. If necessary, they will be referred for additional follow-up by their private physician.

The referral cutpoint for LDL-C is based on the 1991 NCEP guidelines for consideration of drug therapy in children and adolescents. During the in-clinic review, the clinic physician will determine if referral is warranted based on the level of the LDL-C value and the presence of two or more other CHD risk factors (smoking, family history, low HDL-C, high blood pressure, obesity and/or diabetes).

Referral Cutpoint

LDL-Cholesterol	> 160 mg/dl
Triglycerides	> 200 mg/dl

All participants will receive their lipid values so that they may provide the information to their physician to aid the physician in providing usual care.

I. BLOOD PRESSURE MONITORING

I.1 Introduction

Blood pressure will be monitored for the development of hypertension using the blood pressure measurements obtained during follow-up.

I.2 Monitoring for Elevated Blood Pressure in the DISC Study Population

The monitoring for elevated blood pressure in the DISC study population will follow the guidelines outlined by the Second Task Force on Blood Pressure Control in Participants (Pediatrics 1987; 79:1-25) as outlined in the table.

Classification of Hypertension by Age Group

6 - 9 Years	Systolic BP => 122 mm Hg Diastolic BP => 76 mm Hg (4th Korotkoff's sound)
10 - 12 Years	Systolic BP => 126 mm Hg Diastolic BP => 82 mm Hg (4th Korotkoff's sound)
13 - 15 Years	Systolic BP => 136 mm Hg Diastolic BP => 86 mm Hg (5th Korotkoff's sound)
16 - 18 Years	Systolic BP => 142 mm Hg Diastolic BP => 92 mm Hg (5th Korotkoff's sound)

The blood pressure used for monitoring hypertension in the DISC study population is the mean of the two blood pressures measured at the clinic visit. If a participant's blood pressure matches or exceeds the defined cutpoints, the participant will have a Clinical Monitoring Form and in-clinic review initiated. If necessary, they will be referred for further evaluation by their private physician.

J. PSYCHOSOCIAL MONITORING

J.1 Introduction

The DISC Psychosocial Subcommittee has recommended the use of published clinical cutpoints for clinical monitoring or has recommended other criteria when no published standards are available. Five areas of psychological safety will be monitored: depression, suicide, behavior problems, anxiety and eating disorders.

All participants classified as "possible anorexic" or "possible bulimic" are to have a Clinical Monitoring Form initiated and be reviewed by the clinic psychologist. He/she will decide if a referral is indicated, who will contact the family, and whether this will be done by telephone or in person. The family is then to be contacted and further information elicited. If appropriate, the participant will be

referred for further evaluation by the participant's private physician or psychologist.

All participants who exceed the established cutpoints for depression, suicide, anxiety or total behavior problem score will have a Clinical Monitoring Form initiated and will undergo clinical review as soon as possible by the DISC clinic psychologist. If the clinic psychologist feels that a referral is warranted, a referral will be made for further evaluation by their private physician.

J.2 Depression

The published clinical cutpoint for the participant's Kovacs Depression Inventory (CDI) is a total score greater than 14. The published clinical cutpoint for the Beck Depression Inventory (Beck Form) is a total score of greater than 19.

J.3 Suicide

The clinical cutpoints for suicide recommended by the DISC behaviorists are as follows: a "Yes" to question 9C on the Kovacs CDI ("I want to kill myself"); a "Somewhat or Sometimes True" or "Very true or Often True" checked by either parent on the Achenbach Child Behavior Checklist (CBCL) question 18 ("Deliberately harms self or attempts suicide") or question 91 ("Talks about killing self"); an answer of 2 or 3 to questions 2 (hopelessness) or 9 (suicide ideation) on the Beck Depression Inventory (Beck Form); an answer of "Somewhat or Sometimes True" or "Very True or Often True" checked by the participant on the Achenbach Youth Self Report (YSR) question 18 ("I deliberately try to hurt or kill myself.") or question 91 ("I think about killing myself.").

J.4 Behavioral Problems

The published clinical cutpoint for the Achenbach CBCL is a total behavior problem score greater than the 90th percentile for the questionnaire completed by either parent. The published clinical cutpoint for the Achenbach YSR is a total behavior problem score greater than the 90th percentile or T=63.

J.5 Anxiety

The clinical cutpoint for the Spielberger Trait Anxiety Inventory for Children (STAIC - Form C2) was set at 1 standard deviation above the normative mean, or 45, for the total trait anxiety score. The clinical cutpoint for the Spielberger Trait Anxiety Inventory for Adults (STAI-Form Y2) was set at greater than 52 for the total trait anxiety score.

J.6 Eating Disorders

The Clinical Monitoring Committee has given careful consideration to the issue of screening to detect incipient eating disorders among DISC participants. A key consideration has involved the availability of existing, standard instruments that might be used for screening purposes. Unfortunately, the two existing instruments (the Eating Disorders Inventory; the Eating Attitudes Test) have not been studied extensively with adolescents and are both time-consuming and likely to yield high levels of false positives (Williams, R.L.: Use of the Eating Attitudes Test and Eating Disorder Inventory in Adolescents. Journal of Adolescent Health Care, 1987, 8 266-272).

As a result, a screening process that does not involve the use of eating disorders questionnaires seems most suitable. The process will use a question taken from the NGHS study which will be included on the DISC physical exam form. This item will be completed by all DISC participants, and be used to screen for participants who may be

developing symptoms of either anorexia nervosa or bulimia. The question is:

During the past 30 days, did you do any of the following things to lose weight or to keep from gaining weight?

- A. I did not try to lose weight or keep from gaining weight.
- B. I dieted.
- C. I ate very little for one or more days.
- D. I exercised to lose weight or keep from gaining weight.
- E. I made myself throw up.
- F. I took diet pills.
- G. I used laxatives, Ipecac, or diuretics.
- H. I used diet drinks such as Slim Fast.
- I. I used some other method (specify):

Each item is answered "Yes" or "No".

J.7 Screening for Anorexia Nervosa

A participant will be identified as "possible anorexic" if he or she meets two criteria:

1. The participant must be classified as having "worrisome" or "alert" weight for height according to the standards for the clinical monitoring of % IBW (See Section C.3);
2. If so classified, then the screening question from the physical exam form will be reviewed. If the participant answered "Yes" to any item (other than A), the participant will be classified as "possible anorexic".

J.8 Screening for Bulimia

Since bulimia can develop in a participant or adolescent who exhibits normal weight, the weight monitoring aspect of anorexia

screening cannot be used. Instead, all participants who answer "Yes" to the item "I made myself throw up" (Item E) will be classified as "possible bulimic".

K. CLINICAL MONITORING OF PARENTS/ADULTS

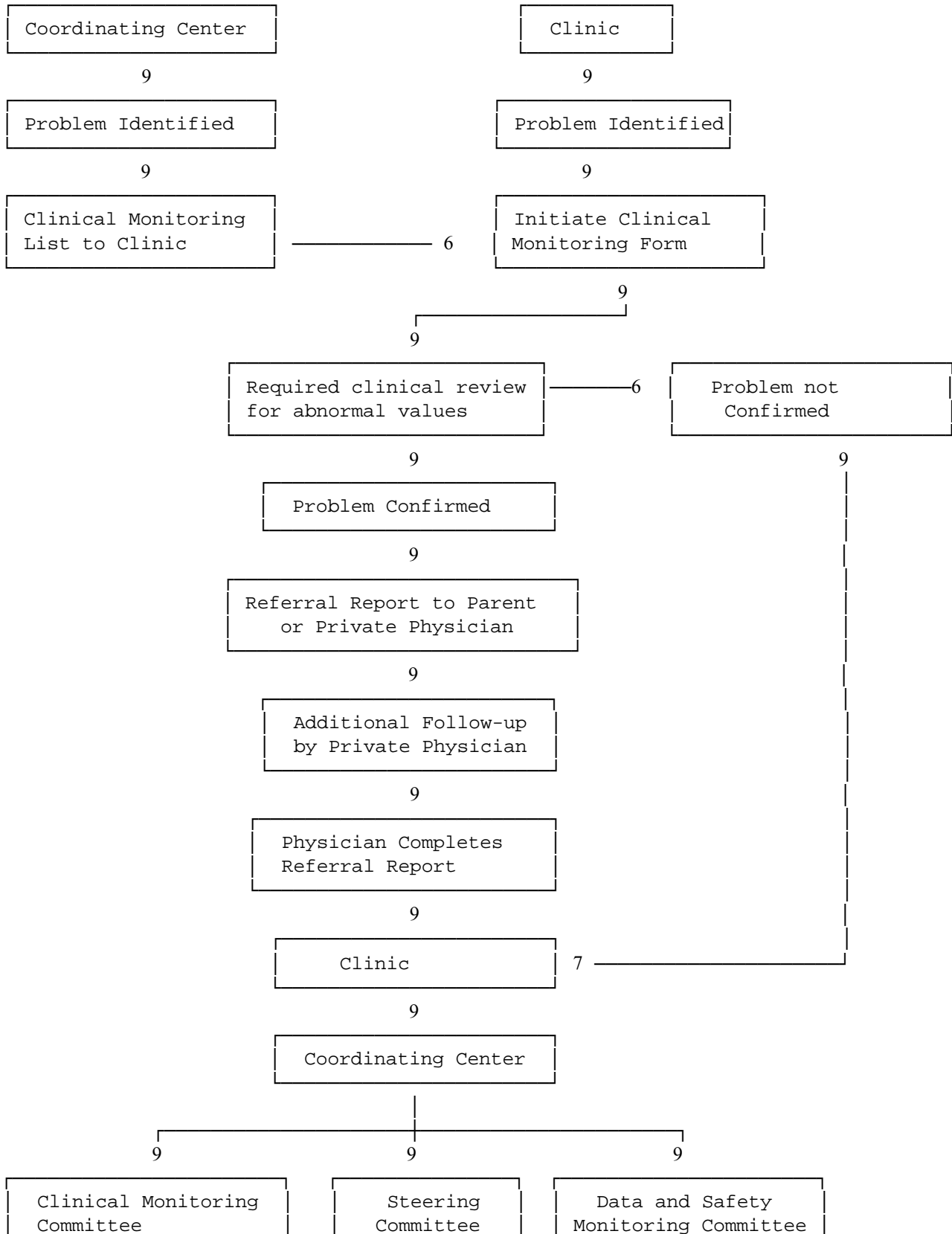
Parents of the participants are assessed at the 36 month visit for elevated blood pressure and for elevated lipid levels. DISC will initiate a Clinical Monitoring Form and refer parents for evaluation of possible medical problems related to elevated total cholesterol or to elevated blood pressure. In screening the parents for these possible medical problems, DISC will follow the guidelines issued by the National Cholesterol Education Program Expert Panel (JAMA, 1993, 269, 3015-3023), and by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (National High Blood Pressure Education Program, The Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, National Heart, Lung, and Blood Institute, NIH Pub. No 93-1088).

	Cut point
Total Cholesterol;	> 240 mg/dl
Diastolic Blood Pressure:	=> 90 mm Hg
Systolic Blood Pressure	=> 140 mm Hg

If the measurements for the parent exceed the defined cutpoints, he or she will have a Clinical Monitoring Form and in-clinic review initiated. If necessary, they will be referred and advised to seek evaluation and remeasurement by their own physician. The physician will be requested to return the Referral Report to the Clinic to report the outcome of the assessment.

FIGURE 1

DISC CLINICAL MONITORING SYSTEM



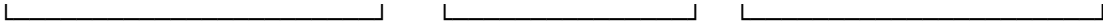


FIGURE 2

HEIGHT VELOCITY CHART FOR BOYS
(Tanner and Whitehouse, 1976)

FIGURE 3

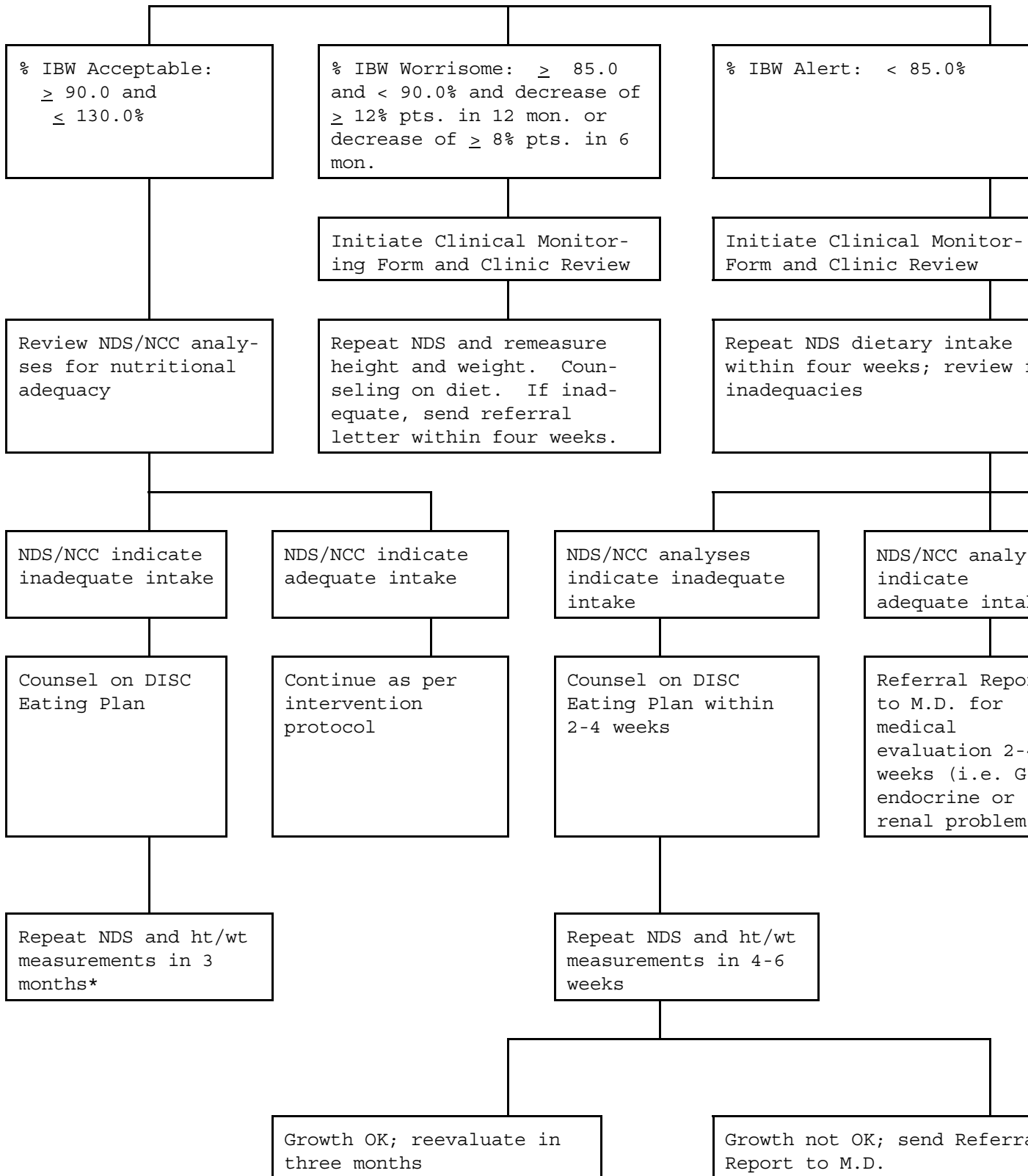
CONSTRUCTION OF LONGITUDINAL STANDARDS FOR HEIGHT VELOCITY
(Tanner and Whitehouse, 1976)

FIGURE 4

HEIGHT VELOCITY CHART FOR GIRLS
(Tanner and Whitehouse, 1976)

FIGURE 5

% IBW EVALUATION AND TREATMENT FOR INTERVENTION PARTICIPANTS

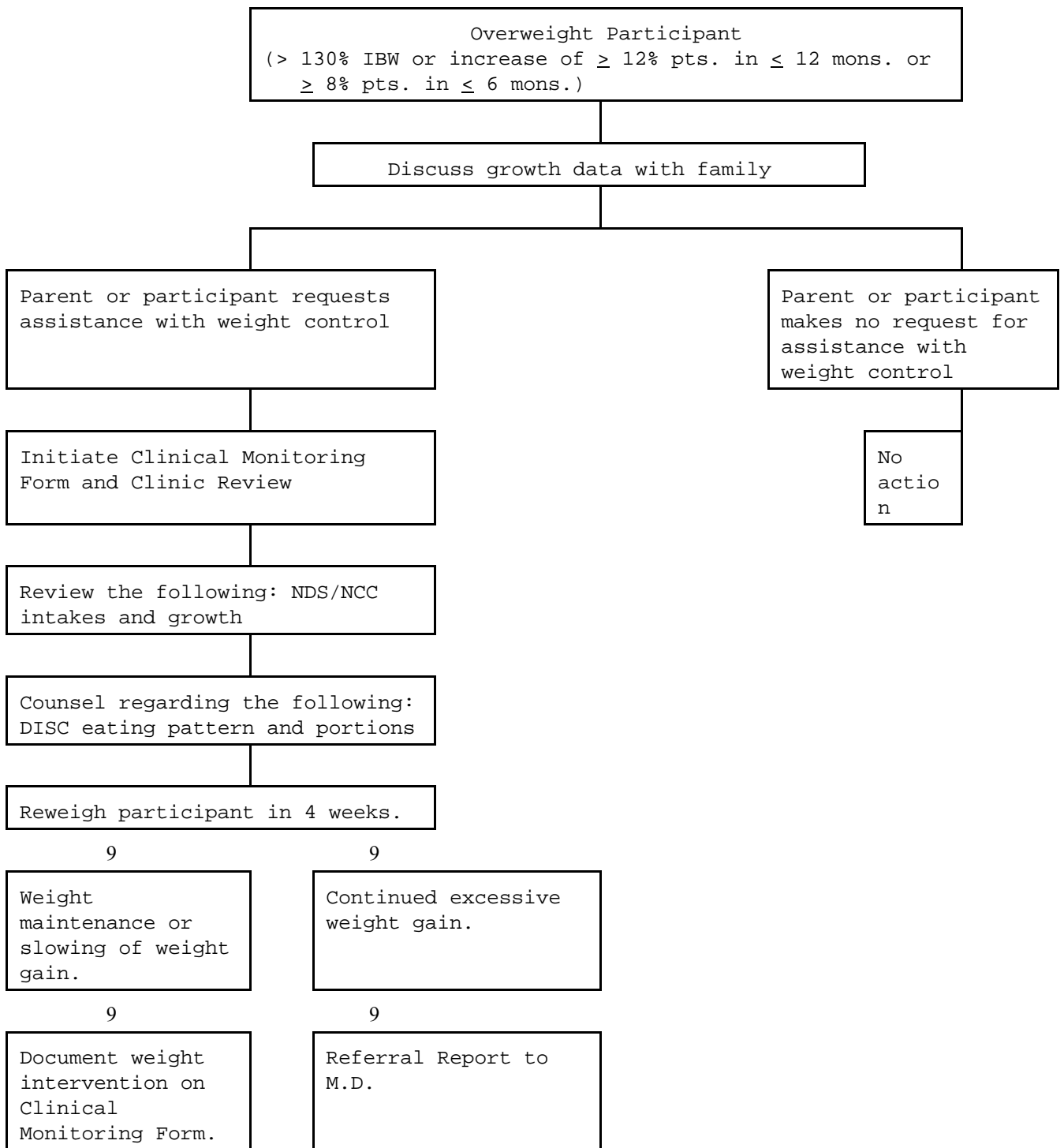


*For a participant who is growing normally and who has received repeat dietary counseling to correct nutritional inadequacies, no extra NDS analyses are required.

*For a participant who is growing normally and who has received repeat dietary counseling to correct nutritional inadequacies, no extra NDS analyses are required.

FIGURE 6

HIGH % IBW EVALUATION AND TREATMENT FOR INTERVENTION CHILDREN



Summary Table
Clinical Monitoring Cutpoints

1. Height Velocity	1 Year	2 Years
Boys (9-13)	< 3 cm	< 8 cm
Girls (8-11)	< 3 cm	< 8 cm
2. % IBW	<p>Worrisome: 85% ≤ % IBW < 90% and decrease of > 12 percentage pts. /12 months or ≥ 8 percentage pts. /6 months</p> <p>Alert: % IBW < 85%</p> <p>Overweight: % IBW > 130% or gain of ≥ 12 percentage pts. /12 months</p>	
or	<p>≥ 8 percentage pts. /6 months (Intervention Only)</p>	
3. Pubertal Stages		
<u>Girls Stage:</u>	<u>Should reach stage by:</u>	
Breast II	13 years	
Breast IV	15.3 years	
Pubic hair II	13.4 years	
Pubic hair IV	15 years	
Menarche	15 years	
<u>Boys Stage:</u>	<u>Should reach stage by:</u>	
Testes 4 ml	13.5 years	
Testes 12 ml	16.5 years	
Pubic hair II	14 years	
Pubic hair IV	16 years	
4. Menstrual Bleeding	> 10 consecutive days	
5. Hemoglobin	< 11 g/dl or decrease of 1.5 g/dl between last 2 measurements	
6. Ferritin	< 7 ng/ml	

7. Blood Chemistry Monitoring Cutpoints

Variable	Lower Limit	Upper Limit
Albumin	3.1	5.8
Total Protein	5.5	8.8
SGPT (ALT)	--	67.5
SGOT (AST)	--	76.3
Glucose	50.0	110.0
Urea Nitrogen	--	25.8
Creatinine	--	1.1
Total Bilirubin	--	1.4
Direct Bilirubin	--	0.5
Calcium	7.4	11.1
Phosphorus	2.4	7.1
Uric Acid	1.1	6.4

8. Blood Lipids

<u>Cutpoint</u>		<u>Referral</u>
mg/dl	LDL-Cholesterol:	> 160
mg/dl	Triglycerides:	> 200

9. Blood Pressure

Classification of Hypertension by Age Group

6 - 9 Years:	Systolic BP => 122 mm Hg Diastolic BP => 76 mm Hg (K4)
10 - 12 Years:	Systolic BP => 126 mm Hg Diastolic BP => 82 mm Hg (K4)
13 - 15 Years:	Systolic BP => 136 mm Hg Diastolic BP => 86 mm Hg (K5)
16 - 18 Years:	Systolic BP => 142 mm Hg Diastolic BP => 92 mm Hg (K5)

10. Psychosocial Scales

Depression:	CDI > 14 Beck Form > 19
Suicide:	CDI Ques. 9C = Yes Beck Form Ques. 2 = 2 or 3 Beck Form Ques. 9 = 2 or 3 Achenbach (CBCL) Ques. 18 = Somewhat or Very True (either parent) Achenbach (CBCL) Ques. 91 = Somewhat or Very True (either parent) Achenbach (YSR) Ques. 18 = Somewhat or Very True (participant) Achenbach (YSR) Ques. 91 = Somewhat or Very True (participant)
Behavior Problems:	Achenbach (CBCL) Total Behavior Problem Score > 90th % Achenbach (YSR) Total Behavior Problem Score > 90th %
Anxiety:	STAIC Total Trait Anxiety Score > 45 STAIC (Self-Evaluation Form) Total Trait Anxiety Score > 52
Eating Disorders:	
Anorexia -	Worrisome/alert % IBW and any item from screening question = Yes (except Item A)*
Bulimia -	Screening question = Yes (Item E)*

11. Parent Measurements

Total Cholesterol:	> 240 mg/dl
Systolic BP:	≥ 140 mm Hg
Diastolic BP:	≥ 90 mm Hg

*During the past 30 days, did you do any of the following things to lose weight or to keep from gaining weight?

- A. I did not try to lose weight or keep from gaining weight.
- B. I dieted.
- C. I ate very little for one or more days.
- D. I exercised to lose weight or keep from gaining weight.
- E. I made myself throw up.

- F. I took diet pills.
- G. I used laxatives, Ipecac, or diuretics.
- H. I used diet drinks such as Slim Fast.
- I. I used some other method (specify):

Appendix A

Appendix A Selection of Height Velocity
Cutpoint

Figures 2-4, taken from Tanner [ref: JM Tanner and RH Whitehouse, Atlas of Participants's Growth, Normal Variation and Growth Disorders, London, Academic Press 1982] were used as the basis for these cutpoints. The marked, unshaded percentiles represent the situation for the cohort of boys (or girls) all of whom have their peak height velocity at exactly the average age for the event (boys: 14.0 years; girls: 12.0 years). The 95% range over which the peak occurs extends 1.8 years before and 1.8 years after the central age. The shaded percentiles represent the situations for the cohorts of boys who matured 2 SD early and 2 SD late. Figure 3 illustrates how these shaded areas were constructed. Early - maturing boys have a higher peak height velocity than boys who mature at an average age and late maturing boys have a lower peak velocity. Both the shaded areas of Figure 3 have been put in Figure 2. The symbols in Figure 2 represent the 97th, 50th and 3rd

percentiles of peak height velocity when the peaks take place 1.8 years early and 1.8 years late. Thus early maturing boys have curves which fall within the shaded area to the left of the central peak and late maturing boys have curves falling the shaded area to the right of the peak. The curve for height velocity in girls is shown in Figure 4. Curves which fall outside the shaded areas in Figure 2 or Figure 4 are abnormal either in intensity or in timing or both. Thus, the 3rd percentiles in Figure 2 and Figure 4 were selected as cutpoints.

CHAPTER 10

THE HORMONE STUDY

10.1 Organization

The hormone study in DISC is being conducted in collaboration with the National Cancer Institute (NCI).

10.2 Background

Sex hormones may play an important role in the etiology of cancer, particularly breast and prostate cancers. Diet, especially dietary fat intake, also has been implicated in the etiologies of breast and prostate cancers. A current hypothesis is that diet influences the risk of these cancers through its affect on the hormonal milieu.

Adolescence may be a particularly vulnerable time for exposure of the breast to carcinogens. Numerous experts, therefore, have recommended that adolescent exposures be investigated in relation to cancer risk.¹⁻³ Because of the long time from exposure during adolescence to diagnosis of cancer in adulthood, cancer is an unrealistic endpoint for clinical trials initiated during childhood and adolescence. Studying the effects of diet and other exposures on hormones that have been associated with cancers and with known risk factors for these cancers, is a realistic alternative.

10.3 Objectives

This hormone study will enable us to explore hypotheses about adolescent exposures and cancer risk. The specific objectives of the study are as follow:

Primary

To determine the effect of a fat-modified diet on endogenous sex hormones and the bioavailability of these hormones during adolescence.

Secondary

To assess the associations of age, Tanner stage, anthropometric measures, physical activity, food patterns, and nutrient intake with levels of endogenous hormones and the bioavailability of these hormones;

To assess the associations of diet, anthropometric measures, and physical activity with sexual maturation and, in girls, age at menarche.

To assess the associations of diet, anthropometric measures, and physical activity with menstrual cycle length and the frequency of anovulatory menstrual cycles in post-menarcheal girls.

10.4 Design

The hormone study will be integrated into the main trial. An additional 2.5 mls of serum will be collected at the baseline screening visit 2 and at the 12-month follow-up visit from participants who had not completed these visits prior to initiation of the hormone study. At the 36- and 37-months visits, an additional 2.5 mls of serum will be collected from all participants, and at the Year 5, Year 7, Year 9 visits, and the final two visits at 18 years of age an additional 5 mls of serum will be collected from all participants for the hormone study.

Questions about menarche will be asked at all clinic visits until girls have begun menstruating. Beginning at the 36-month clinic visit,

girls who have reached menarche will complete menses calendars for 6 weeks before and 6 weeks after each clinic visit that includes a blood draw.

Hormone assays will be performed under a NCI contract. Table 10.1 lists the hormones to be assayed by clinic visit for girls and boys. A ten percent sample of blind duplicates will be assayed with specimens for quality assurance.

Table 10.1 Hormone Assays to be Performed on Serum from Girls and Boys by Visit

Visit	Girls	Boys
Baseline & 12 months	estradiol estrone SHBG non-SHBG-bound estradiol	testosterone SHBG non-SHBG-bound testosterone
36 & 37 months	estradiol estrone SHBG non-SHBG-bound estradiol progesterone	testosterone SHBG non-SHBG-bound testosterone dihydrotestosterone
Years 5, 7, 9 & 18 years of age	estradiol estrone SHBG non-SHBG-bound estradiol progesterone androstenedione DHEAS estrone sulfate testosterone	testosterone SHBG non-SHBG-bound testosterone dihydrotestosterone androstenedione DHEAS estradiol estrone

SHBG = sex hormone binding globulin; DHEAS = dehydroepiandrosterone sulfate.

10.5 Analysis Plan

(To be added after approval.)

References

1. Cole P, MacMahon B. Oestrogen fractions during early reproductive life in the aetiology of breast cancer. *Lancet* 1969;2:604-6.
2. de Waard F, Trichopoulos D. A unifying concept of the aetiology of breast cancer. *Int J Cancer* 1988;41:666-9.
3. Kelsey J, Berkowitz G. Breast cancer epidemiology. *Cancer Res* 1988;48:5616-23.

CHAPTER 11

PARTICIPANT FOLLOW-UP

11.1 Introduction

One of the most crucial aspects of achieving a successful study involves making every effort to keep the intervention group participants returning for the intervention sessions and participants in both groups returning for their periodic data collection visits. Missing the intervention sessions will result in reduced compliance to the dietary regimen, and missing the data collection visits will potentially lead to bias in assessment of the efficacy and safety outcomes between the two treatment groups. This chapter discusses appointment schedules, missed appointments, incentives for maintaining participation, maintenance of contact with study participants, missed visits, study dropouts, and transfer to other Clinical Centers.

11.2 Time Windows for Follow-up Data Collection Visits

The Coordinating Center will generate a listing of the time frames for the follow-up data collection visits for each Clinical Center annually. The scheduled dates for follow-up data collection visits will be computed at 6-month or annual intervals from the date of entry into the study, i.e., the date of transmission of the treatment allocation. In addition to the expected dates, the time limits within which each visit must be completed in order to be considered a valid visit will also be specified. The acceptable time window for completing the 6-month visit is ± 1 month from the expected date. The acceptable time window for completing the 12, 24, 36, 48, 60, 72, 84, 96, 108 month and final visits is ± 2 months from the expected date.

11.3 Missed Appointments

Whenever a DISC participant fails to keep an appointment for a regularly scheduled visit, steps to bring the participant back to the clinic will be initiated promptly. In some cases a phone call or note in the mail from the clinic nurse/coordinator stressing the importance of complete follow-up may be sufficient. Some participants and/or their parents may respond more favorably to a call from the study physician or from a home visit. Help in arranging transportation will be offered, including payment of travel costs, if necessary. Participants who are unable to visit the clinic during regular clinic hours may be willing to make a visit on a weekend, in the evening, or at another time. Willingness to be flexible and eagerness to see the participant, even though the desired day or time may be inconvenient, are positive demonstrations of the importance placed on follow-up and should help to improve cooperation of the participants and their families.

11.4 Incentives for Maintaining Participation

A number of incentives will be offered the DISC children and their parents in order to encourage their continued cooperation and participation in the trial. For intervention group children and their parents there will be free meals at some of the intervention sessions, tape recorders for recording the 3-day dietary records, and the offer of free cholesterol determinations (using the DT-60 desktop analyzer) at the intervention sessions as well as at the data collection visits.

Furthermore, clinic coordinators will be encouraged to send birthday cards and other greeting cards to the children and their families at their discretion. Special arrangements will be made for VIP parking

privileges if possible, and waiting times at the clinic visits will be minimized. In cases where transportation to the clinic or paying a baby sitter are financial hardships, reimbursement for these expenses will be provided.

11.5 Maintenance of Contact with Participants

At the time of the randomization visit, the DISC children and their parents will be asked to provide the names, addresses, and telephone numbers of their family physician, the parents' employer(s), and at least two other persons not in the same household who would be likely to know the family's whereabouts two or three years later. This information will be updated at the 36-month visits. In case the family moves away without leaving a forwarding address, this information will be useful in attempting to regain contact with the family.

The participant's address, telephone number, and plans to move in the next 12 months will be updated at each data collection visit. In addition, since control group participants will be seen less regularly than those in the intervention group, post cards will be sent to control group participants six months before annual data collection visits to update addresses and telephone numbers and to ask if there are any plans to move in the next six months.

At the 36 month data collection visit parents will be asked to provide the child's Social Security number.

11.6 Missed Visits

If a regularly scheduled DISC follow-up data collection visit cannot be completed within the time period specified for the visit, an attempt will be made to schedule another visit no later than halfway between the expected date of the presently scheduled visit and the next

scheduled visit. For example, if the 12-month visit is not completed within 14 months of the date of entry, an attempt will be made to reschedule it within 18 months of the date of entry. A follow-up visit completed outside the time period specified for an annual data collection visit but within the broader window just described will be classed as "completed outside time window." Visits not completed within the broader (i.e., ± 3 or ± 6 months) windows will be classed as "missed visits" and such visits cannot be made up by the participant. Special exceptions to window requirements for endpoint data collection visits at 36 months and the final visit will be made. For the 36-month visit, if the participant cannot be seen within the visit window, the 36-month information should be obtained at any time the participant is seen subsequent to the missed visit, even if this occurs closer to the 48-month or 60-month visit window. Under these circumstances, the Coordinating Center should be contacted as to the appropriate forms to use.

The primary data analyses will be done on visits completed within the narrower (i.e., 1-month and 2-month) time windows. Information obtained at visits completed outside the time windows will be available as a fallback measure if there is too much missing data.

11.7 Study Dropouts

For the purposes of DISC, a dropout is defined as a study participant who no longer reports to the DISC Clinical Center for follow-up data collection visits. This definition includes those individuals who have moved out of the area and are unable to participate in the study, as well as those who remain in the area but are not willing or able to continue active participation. This definition does not include those

who no longer are willing or able to attend intervention sessions. Nor does it include those who can no longer follow the DISC dietary regimen due to adverse effects or other reasons. Those in these latter categories will be strongly urged to continue attending the data collection visits.

If a study dropout still lives in the area of the Clinical Center, periodic attempts will be made to renew his/her participation in the study, at least in the data collection visits if not the intervention sessions. Special attempts will be made to re-contact inactive participants for endpoint data collection visits at 36 months and the final visit. If they are willing to participate but will not come to the clinic, the possibility of taking stadiometer, scale, and venipuncture to the homes of such participants and measuring height and weight and collecting a blood sample will be offered.

If the participant has moved to an area of another DISC Clinical Center, the family will be asked to transfer to the Clinical Center near their new home (see Section 11.8 below). If no DISC clinic is nearby, special arrangements for measurement and blood draw at a non-DISC medical facility will be made.

If a study dropout later agrees to return to the study, he/she will be asked to complete the appropriate follow-up visit indicated for that time period. If the 1- or 2-month time window for the last scheduled visit is past, then the broader, 3-month or 6-month, window may still be applied to complete the visit. For endpoint data collection visits at 36 months and the final visit, see page 11-4 and the Manual of Operations Chapter 4 for special exceptions to window requirements.

11.8 Transfer to a New Clinical Center

If the participant moves to an area in which another DISC Clinical Center is located, the former Clinic will assist the participant's family in contacting the new Clinic. The former Clinic will also notify the new Clinic of this potential transfer so that the new Clinic can initiate contact with the family.

The Coordinating Center will not officially transfer a participant until a follow-up visit form is received from the new Clinic. If a participant does not agree to participate in the new Clinic, he/she becomes a dropout and remains the responsibility of the former Clinic with respect to any follow-up contacts and clinic-specific data analyses.

8/18/94

CHAPTER 12

TRAINING, CERTIFICATION, AND RECERTIFICATION

12.1 Training

In a collaborative study with multiple Clinical Centers collecting data, it is important that the personnel performing similar tasks among the field centers all be trained in a uniform manner to carry out those tasks. Thus, for certain data collection tasks in DISC -- e.g., anthropometric measurements, blood pressure measurements, psychosocial and dietary assessment interviews -- as well as for other tasks such as preparation of laboratory specimens, the DISC Coordinating Center, in concert with the NHLBI Project Office and the Clinical Center investigators, will conduct a series of training sessions prior to the beginning of data collection in DISC. Personnel who join the study after its initiation will generally be trained by the local Clinical Center master trainer for a given task. However, if several persons from different Clinical Centers require training at about the same time (such as at the beginning of a new school year), it may be expeditious to have them all trained centrally at one session.

Since the DISC full-scale trial is a ten-year study, a single certification prior to the beginning of the study will not suffice. Periodic recertification, at least annually, will be required for most tasks for which certification is required.

The Clinical Center itself must be certified before data collection can begin. To be certified, a Clinical Center must have at least one certified person to do each task requiring certification and

provide evidence of satisfactorily adhering to inspection and maintenance procedures for all equipment. All field centers must be recertified periodically.

Special training, using uniform training methods and common training materials will be required for the following tasks:

1. Anthropometric measurement
2. Blood pressure measurement
3. Blood specimen preparation
4. Dietary assessment
5. General interviewing
6. Maturity staging
7. Psychosocial assessment except Woodcock-Johnson
8. Woodcock-Johnson administration
9. Physical activity recall debriefing
10. Menses data collection

The training sessions will be conducted by persons with extensive experience in carrying out the tasks in the context of similar research projects. Such a person should also, preferably, have had experience training others in the particular task. At each Clinical Center, if more than one person is trained and certified for a particular task at a training session, one of those persons will be designated as the master trainer. To qualify for designation as master trainer, one must have attended a training session and satisfied all criteria for master trainers in that area as described in the DISC Manual of Operations. Personnel who join a DISC Clinical Center after the study is underway must either be trained at a special DISC training session, or by the local Clinical Center master trainer.

12.2 Certification/Recertification

Each person trained in one or more of the tasks listed in Section 12.1.1 above must be certified in that task before he/she can be permitted to carry out that task in DISC. A person may be certified in several tasks; such a person may be designated as a master trainer of one or more of those tasks, but not necessarily as a master trainer of all of the tasks in which he/she is certified. A person certified in one task may not carry out another task in DISC for which he/she has not been certified.

All persons desiring to be certified for one of the tasks listed in Section 12.1 must, as a minimum, either attend a DISC training session for that task or receive training from a DISC master trainer for that task. Certification in a particular task may entail other specific requirements, such as successfully completing test blood pressure tapes for the task of blood pressure measurement. More detailed training procedures and specific requirements for certification in each task will be given in the DISC Manual of Operations.

Annual recertification will be required for most of the tasks listed in Section 12.1. Recertification of all DISC personnel will take place during the month of January of each year of the study. If a new staff member has just been certified initially during November or December, it will not be necessary for that person to be recertified until January of the following year.

DISC data forms require identification of the person who has measured, observed, or collected each type of information, and the

Coordinating Center will routinely check to make sure that the persons who have collected or keyed the information are properly certified.

12.3 Equipment Inspection and Maintenance

Detailed procedures for periodic inspection and maintenance of key measurement instruments used by the Clinical Centers will be provided in the DISC Manual of Operations. Types of equipment for which these procedures must be followed include random zero mercury sphygmomanometers, stature measuring boards, electronic scales, and skinfold calipers. A DISC Equipment Inspection and Maintenance Log will be used for recording and carrying out these procedures. These logs will be reviewed annually by the Study Master Trainers at the annual recertification.

12.4 Certification/Recertification of Clinical Centers

In addition to individual persons being certified to carry out specific tasks in DISC, each Clinical Center as a whole must also be certified before data collection can be initiated at that center and must be periodically recertified. In order for a Clinical Center to be certified/recertified, at least one person in that clinic must be certified/recertified for each of the tasks that require certification.

In addition, for recertification of a Clinical Center, there must be evidence of satisfactory adherence to equipment inspection and maintenance procedures. Clinical Center recertification will take place once a year during the month of January.

CHAPTER 13

QUALITY ASSESSMENT

13.1 Introduction

A primary concern of DISC will be to assure the quality of the data being collected and analyzed. The validity of the reports and results produced and published by the study will depend upon the integrity of the data submitted by the Clinical Centers, Central laboratory, and Nutrition Coding Center, and upon the appropriateness, thoroughness, and correctness of the data processing and data analysis procedures carried out at the Coordinating Center. The first step in assuring quality data is to have the data collectors and measurers properly trained, certified, and periodically recertified (see Chapter 12). This step will then be supplemented with various procedures to monitor the performance of these groups with respect to the quality of the study data reported by them. Procedures for monitoring the performance of the Clinical centers, Central Laboratory, Nutrition Coding Center, and Coordinating Center are given in the following sections.

13.2 Quality Assessment of the Clinical Centers

Performance of the Clinical Centers will be assessed by periodic consideration of the following:

1. Number of participants enrolled to date and ratio of this number to the number who should have been enrolled to date given the scheduled recruitment period already completed.

2. Percentage of participants with missed examinations and percentage who are no longer willing or able to have their annual examinations.
3. Number of study forms for which the data are past due at the Coordinating Center based on each participant's date of randomization. For this purpose it is necessary to define a time window for completion of each annual exam. It will cover two months on either side of the anniversary of the date of randomization.
4. Number of protocol violations, such as enrolling participants who do not meet all of the eligibility criteria or who have not provided informed consent, or performing follow-up exams outside the proper time window.

These monitoring activities will be supplemented by periodic site visits by site visit teams to the Clinical Centers, and by annual recertification of Clinical Center personnel responsible for key areas of data collection and entry,.

13.3 Quality Control of Anthropometry Measurements

The primary safety outcome monitored during DISC will be attained height. In addition to standardized training and procedures for height and other anthropometric measurements, the Coordinating Center will prepare periodic quality control reports on height measurement. These reports will analyze recent height measurements at each Clinical Center for indications of problems with measurement technique. These reports will examine the data for indications of observers with digit preferences, and for differences between observers in the mean heights recorded which could indicate systematic differences in how

measurements are performed. Quality control reports for each examination cycle will be timed to allow clinics to take corrective action before the examination cycle is completed if problems are detected.

13.4 Quality Assessment of the Central Laboratory

The purpose of a Central Laboratory for a multicenter longitudinal study like DISC is twofold: (1) to provide biochemical determinations in a uniform manner on specimens received from several different Clinical Centers; and (2) to provide determinations that are stable over a period of several years. The Central Laboratory for this study has agreed to use the same analytical methods and equipment throughout the course of the study, and to participate in the Centers for Disease Control Quality Assurance Program for Lipid Determinations as well as in other national quality assurance programs for other types of determinations. The Central Laboratory has also agreed to send the Coordinating Center, at periodic intervals, quality control reports on each study determination, including special events such as a change of standard and control pools, and a change of reagents, instrument failures, number of runs out of control, etc.

The Coordinating Center will establish an external quality assessment program for the Central Laboratory that will require the Clinical Centers to obtain an additional amount of blood from a random sample of participants throughout the course of the study and to submit duplicate specimens to the laboratory in separate shipments. Procedures for carrying out such programs, including the blinding of the identity of the duplicate specimens to the Central Laboratory are well established.¹

13.5 Quality Assessment of Nutrition Coding

Three-day random dietary recalls will be collected at baseline on the children in DISC. These recalls will be sent to the Nutrition Coding Center for coding, keying, and nutrient analysis. In addition

to the Nutrition Coding Center's own internal quality control programs, an external quality control program will be established by the DISC Coordinating Center. It will check periodically on the validity and reliability of the nutrient coding by sending to the Nutrition Coding Center, in a blinded fashion, DISC participant food recalls previously coded at their Center.

13.6 Quality Assessment of the Coordinating Center

In spite of the difficulties of self-monitoring, the following are some of the activities the DISC Coordinating Center will carry out that will help to enhance the quality of the data and analyses:

- 1.A sample of original data forms will be compared with the data entered on computer to detect problems with the data entry and editing software and problems with merging the data onto the main study data base.
- 2.For each variable on the data base a point frequency distribution -- i.e., a tabulation of the frequency of occurrence of every distinct value -- will be obtained. This will help to identify many types of anomalies in the data such as: (a) illegal codes, (b) measurements given to more decimal places than provided by the measuring instrument, (c) digit preferences, (d) bimodality or other bizarre form of the distribution, and (e) outliers, i.e., extreme values distinctly separate from the rest of the distribution. Once an observation has been identified as a true outlier, the first step is to go back to the original records and determine whether a recording or keying error was made. If such a value is verified as correct, then the question of whether or not to

include the value in the data analysis depends upon the nature of each participant analysis. There is no reason to exclude the value if the analysis is a count of the number of participants having a value exceeding a given cut point. However, if means and standard deviations are being computed, or if correlation or regression analyses are being carried out, and the outlier value is such that it could have an undue impact on the mean and standard deviation, t-test, regression analysis, etc., then it will either be excluded or given a less extreme value (a procedure known by statisticians as Winsorization²) for purposes of the analysis.

3. New analysis programs (including runs using statistical packages such as SAS and BMDP) will be tested by running against a small subfile of 10 or 20 participants and independently producing the tabulations and statistical calculations manually from the original data. This will help to make sure the correct variables have been picked up from the analysis file, the variables and cut-points have been defined properly, transformations of the original variables on the analysis file have been formulated correctly, and the correct variables have been extracted from the main data base onto the analysis file.

4. When preparing data reports, different tables, which may have resulted from a variety of analysis programs, will be checked for consistency of denominators. A discrepancy of as little as one participant among the denominators in different tables may be an indication of a much larger problem.

13.7 Quality Assessment of the Intervention Methods

The quality assessment of intervention methods carried out at the Clinical Centers will involve six major areas, as described in the sections below.

13.7.1 Individual Intervention Sessions

The content of individual intervention sessions will be monitored by gathering data on starting time and duration, personnel involved, topics covered, techniques and education materials used. Any deviations from protocol and the reasons for such deviations will be documented.

13.7.2 Participant Involvement

Participant attendance and activities at intervention sessions will be documented by the notation of the number of sessions attended by the child and other family members. Data will also be gathered on the number of food records kept by the child, the number of assignments completed by the child and other family members, the number of goals written down by the child, and the number of goals attained by the child. A form will be completed for each session by interventionists documenting reasons for not completing specified activities.

13.7.3 Participant Evaluation

An evaluation will be completed by selected Cohort 1 families around the time of the second annual visit in order to evaluate (1) the intervention site-accessibility, safety, time of the sessions and adequacy of the facilities; (2) intervention strategies used, including content, methods of delivery, and educational materials; and (3) personnel, including overall functioning in individual roles, level of

rapport with participants, and perceived level of information and preparation. Participants will be encouraged to explain problems encountered and offer suggested changes in the DISC intervention.

13.7.4 Participant Contact and Follow-up Outside of Regular Sessions

A form will be completed by case managers which will document methods used to remind participants of intervention sessions and to follow-up missed appointments, reasons for missed sessions, and how the session was made up.

13.7.5 Intermediate Participant Outcomes

Evaluations will be done of children and other family members to assess intermediate outcomes in the form of dietary knowledge, skills, perceptions, attitudes and behavior.

13.8 References

- 1.Canner PL, Krol WF, Forman SA: External quality control programs. Controlled Clin Trials 4:441-466, 1983.
- 2.Barnett V, Lewis T: Outliers in Statistical Data. New York, Wiley and Sons, 1978.

CHAPTER 14

DATA MANAGEMENT

14.1 Forms Handling

All data related to the study will be recorded on study forms supplied by the Coordinating Center. Each form will be completed and signed by the person responsible for the information on the form. All forms will be completed in black ink and checked for completeness before the participant leaves the Clinical Center. Each form will then be photocopied and the original will be sent to the Coordinating Center for data processing. The copy of the form will be kept at the Clinical Center for later reference.

At the Coordinating Center, forms will be inventoried immediately upon receipt and then sent to the data entry section for entry into the computer system.

14.2 Data Processing

Each form will be entered twice by different data entry operators and the two entries will be compared electronically. Any discrepancies between the two entries will be printed out for adjudication by the Data Entry Supervisor. After a form has successfully completed the comparison of the two entries, it will be edited for the following problems:

- 1.Values which are not within a predefined 'normal' range, such as a child who weighs 300 pounds. These values will be identified as out-of-range and the clinic will be asked to change the value if incorrect or verify that the value is correct. Questions which have coded answers, such as 1 for

'yes' and 2 for 'no,' will be checked at data entry time to eliminate the entry of invalid codes.

2. Missing information. Any information which should be completed but has not been or any information which has been completed illegibly will be identified as missing and the Clinic will be asked to complete the item.

3. Information which is inconsistent within the form, such as if a fasting blood specimen was obtained but another question on the form indicated that the participant was not fasting. The Clinic will be asked to correct the form.

4. Information which is conditionally inconsistent, such as if the participant said that they were not on prescription drugs but then indicated a drug name. The Clinic will be asked to correct the form.

Any problems identified in this process will be printed out and sent to the Clinics for correction and verification. Information sent back by the clinics will be processed and inserted into the data records. An audit trail, both paper and electronic, will be maintained to keep track of any changes to the forms or to the data files and why those changes were made.

Data from the Central Laboratory and the Nutrition Coding Center will be received electronically and, after appropriate checks of identifying information and validity of the data, will be inserted into the data base.

A number of data management reports will be produced for the Clinics to assist in the maintenance of the quality of the data. These reports will include information on missing forms for a participant, any participants which have not been seen within a specific time period

and information on adherence to the intervention. In addition, recruitment information will be provided during that phase of both the Feasibility Study and the Full-Scale Trial.

14.3 Maintenance of the Data Base

The study data base will be maintained on the mainframe computer housed at the DISC Coordinating Center. The data base will be stored as a hierarchical keyed data base with software written to access the data. The data entry process, which writes into the data base, will enter data into a differential volume, or temporary data base. On a hourly basis, a utility will take the data from the differential volume and insert it into the permanent data base, thereby reducing the exposure to corruption of the permanent data base.

The data base will be archived weekly and an incremental backup of changes or additions to the data base will be done daily.

The computer systems at the Coordinating Center have three levels of security in place to protect all files on the system. Only specified individuals will be allowed to enter data into the data base or to read data from the data base. The data base will be protected from inadvertent deletion from the system through two levels of protection.

CHAPTER 15

ANALYSIS PLANS

15.1 INTRODUCTION

Data analysis will be carried out in this study for two purposes.

The first purpose for data analysis is to seek answers to the research questions and objectives of this study. It is anticipated that research data reports will be generated at annual intervals throughout the study, with the first report generated in November 1988, to analyze the data from the feasibility study.

The second main purpose for data analysis is to monitor the Clinical Centers and other study units for performance with respect to participant recruitment and follow-up, adherence to study protocol, and correctness and completeness of study data, and to evaluate data from external quality control programs. For this purpose, it is anticipated that performance monitoring reports will be generated every three months during the feasibility study and monthly in the full-scale trial. Quality assurance reports will be generated every six months.

15.2 RESEARCH QUESTIONS

15.2.1 Preliminary Analyses

Before beginning analyses directly related to the research objectives of this study, it will be necessary to carry out a number of preliminary analyses of the data. These will include the following:

- 1.Generation of a point frequency distribution (that is, a distribution including each distinct value observed or measured) for each variable on the data base.

2. Detection of outlier values in the univariate data followed by attempts to determine a reason for the extreme values and decisions on how to handle the outlier values in the analyses.
3. Evaluation of skewness and kurtosis of the distributions of each of the continuous variables and an assessment of whether a logarithmic or other 'Gaussianizing' transformation may be warranted.
4. Definition of combinations of variables, such as summary scores for each of the psychosocial scales, a weight for height index, a combined skinfold measure, and index for physical activity, etc.
5. Searching for baseline socioeconomic, nutritional, biochemical, clinical or psychosocial characteristics correlated with treatment group. Such variables will be identified early in the study since they may have a profound effect on the conclusions that can be derived.
6. Generating scatterplots of each dependent-independent variable combination and looking for bivariate outliers.

15.2.2 Feasibility

As described in Section 3.4, the primary outcomes of concern in the feasibility study will be the ability of DISC clinics to recruit children for this study and the ability of the children to adhere to a fat-modified or lipid-lowering diet while maintaining nutritional adequacy.

The ability of the Clinics to recruit children for DISC can be assessed in part by simple comparison of recruitment achieved vs.

recruitment expected (20 per Clinic). Of greater significance for feasibility of the full-scale trial is a determination of the ratios of number screened to number eligible, and number eligible to number who consent to participate. These ratios will then be compared to the populations available to each Clinic to estimate the likelihood of reaching the recruitment goal of 80 participants per Clinic in the full-scale trial.

The ability of the children to adhere to a fat-modified or lipid-lowering diet during the period of intervention will be assessed primarily by means of the dietary intake data obtained on the children at baseline and at selected intervention visits. The dietary goals for the study have been established (Section 8.1.1). Thus, at each visit the amount of reduction (or increase) from baseline in dietary fat intake can be divided by the reduction from baseline level required to achieve the goal, yielding a diet adherence score. The mean score over all follow-up dietary assessments during the feasibility study as well as the score at the end of the feasibility study will be used to assess the child's ability to adhere to the diet over the period of the intervention.

Children's success in maintaining nutritional adequacy will be assessed by comparing the levels of all nutrients reported by the nutrition analysis system from the dietary intake data of the children during follow-up with the baseline values and with the established RDA's for those nutrients.

15.2.3 ANALYSIS PLAN FOR 36-MONTH DATA

15.2.3.1 Primary Efficacy Outcome Measure at 36-Months

Definition

The primary efficacy outcome to be assessed in DISC at 36 months is change in LDL-C from baseline to the 36-month visit. To test for differences in efficacy, a two-sided test is proposed, at $\alpha=0.05$, of $H_0: LDL_{UC}=LDL_I$ versus $H_A: LDL_{UC} \neq LDL_I$, where LDL_{UC} and LDL_I are the mean change in LDL-C in the usual care and intervention groups, respectively. The 36-month LDL-C value will be the average of the LDL-C levels at 36-months and 37-months. The baseline LDL-C value will be the average of the LDL-C levels at SV1 and SV2.

Analysis of the primary efficacy outcome measure will be by "intention to treat" for DISC participants, with all participants included in the group to which they were randomly assigned. This is the approach to be taken in the analysis of the primary outcomes. This approach will assure the validity of the analyses since comparisons made between randomly assigned treatments are unbiased. It is now generally agreed that analyses by 'intention to treat' provides the most unbiased estimate of treatment effect in a clinical trial.¹

Considerations for Intent to Treat Analyses

A total of 663 participants were enrolled in DISC, with 334 assigned to the intervention group (179 males, 155 females) and 329 to usual care (183 males, 146 females). It is anticipated that approximately 90% of the participants will be seen as usual for their 36-month visit and virtually all of these will be seen for the second blood draw one month later. Two problems arise with the intent to treat analysis.

First, what values to impute for those participants who were not seen; and, second, how to handle visits that were completed outside of the visit window.

Imputation Procedures

For the DISC participants for whom LDL-C measurements are not obtained, the following imputation procedures will be employed. LDL-C measurements are quite variable so that earlier LDL-C values (from the 12-month visit) do not offer a firm basis for projecting LDL-C at the 36-month visit². For each missing LDL-C, the mean gender- and Tanner stage-specific LDL-C at the 36-month visit of the opposite treatment group from that to which the participant was originally assigned will be imputed, as suggested by Wittes, Lakatos and Probstfield³. The effect of this procedure is to make it more difficult to reject the null hypothesis and missing data are less likely to lead to false conclusions regarding treatment efficacy. For those participants who had a 36-month blood draw but did not return for a 37-month blood draw, only the 36-month value will be used in the analysis.

Use of Data Collected Outside of the Visit Window

Data which was collected outside of a visit window can still be utilized in a number of ways. For variables which have data available from other visits, linear interpolation will be used to estimate the value at the scheduled (e.g., 36 month) visit time using data from previous visits as well as the data collected outside of the visit window. For all other variables, including other anthropometric measures, lipids, nutrition, physical activity, and psychosocial measures, linear interpolation will be used. Estimating an unknown value, X_t , at time t by linear interpolation can be thought of as estimating X_t by a weighted average of the two measured values closest in time to t , where the weights depend on how distant the time of measurement is to t . Linear interpolation will provide a 'good' approximation to the expected value of X_t if: the time points used for

the interpolation are 'close'; or X_t is approximately a linear function of t ; or X_t varies randomly with respect to t . Linear interpolation will not provide a 'good' approximation if X_t is a strongly curvilinear function of t and the time points used for interpolation are either 'far' apart or poorly spaced with respect to a local minimum or maximum. In the specific case of interpolating the LDL-C value at the 36-month visit, LDL-C values are collected at the MN12, MN36 and MN60 visits. If, for example, the MN36 visit was missed and blood was drawn at the MN48 visit (per the DISC Protocol), then the LDL-C values would be MN12 and MN48. If the study believes that the reasons for missing the MN36 visit were not related to treatment, then interpolation would be acceptable. However, if there is reason to believe that the MN36 visits were missed for reasons related to treatment group, then interpolation was not acceptable. Imputation would have to be used in this case.

Detectable Differences

Calculations are presented below to examine the power of DISC to detect differences between intervention and usual care participants in changes from baseline to 36-month visits for LDL-C (the primary efficacy outcome). While the power calculations are reported for comparison of change scores, assessment of efficacy and safety outcomes at follow-up with analysis of covariance (ANCOVA), using baseline LDL-C as a covariate, or repeated measures analysis will also be considered.

Both analytic approaches will provide a more powerful analysis, but requires a preliminary test of the assumption that no interaction exists between baseline value and treatment⁴. The power estimates presented below are therefore conservative. Because the initial

analyses will be based on intention to treat principals, the first set of estimates are based on the full participant cohort. The second set is based on the assumption that 90% of the cohort will be seen at the 36-month visit.

Let σ be the variance of measurement X at baseline, and σ be the variance of measurement X at 36 months. Let ρ_{12} be the correlation between the measurements of X at baseline and at 36 months. Then the variance of d, the change in X between baseline and 36 months, will be given by $\sigma = \sigma + \sigma - 2\rho_{12}\sigma_1\sigma_2$. Follman⁴ has examined the impact of a single screening at entry on pre- and post-treatment variances. His results are not directly applicable to DISC, due to the more complex DISC entry criteria involving repeated screening for total cholesterol or LDL-C measurements within specified ranges, but do confirm that the common assumption that $\sigma_1 = \sigma_2$ should be avoided. Accordingly, estimates of ρ_{12} , σ_1 , and σ_2 according to gender from DISC baseline and early 36- and 37-month follow-up data are used to calculate power for change in LDL-C.

Let D_{uc} and D_i be, respectively, the mean change from baseline to the 36-month visit for the usual care and the intervention groups. Using the test statistic:

$$T = (D_{uc} - D_i) / \{\sigma[1/n_1 + 1/n_2]\}^{1/2},$$

power for an α -level test to detect a difference, δ , in average change between the two groups may be calculated as $\Phi(-z_\delta)$, where $z_\delta = z_{1-\alpha} - \delta / \{\sigma[1/n_1 + 1/n_2]\}^{1/2}$, and $z_{1-\alpha}$ is the 100(1- α)-th percentile of the standard normal distribution.

Let $z_{\alpha} = 1.96$ for a two-sided test at $\alpha = 0.05$. Thus, DISC will have the following power to detect differences in average change in LDL-C at 36-months for the primary analysis (i.e., intent to treat analysis):

Difference in Average Change in LDL-C (mg/dl)	Power		
	Over-all	Males	Females
1.0	0.11	0.07	0.08
2.0	0.31	0.18	0.19
3.0	0.60	0.35	0.38
4.0	0.84	0.56	0.59
5.0	0.96	0.74	0.78
6.0	0.99	0.88	0.91

The powers listed in this table are probably reasonable estimates of the powers to detect a difference in average change in LDL-C when imputation is used. The imputation procedure would impute a number of identical values which, when combined with the observed LDL-C values, would decrease the variance of the observed LDL-C measures to some extent, depending on the number of values imputed. This would be countered by mean values for the two groups which would not have as large a difference as the difference in the observed LDL-C. The actual effect on the power to detect a difference in LDL-C changes will depend on the number of imputed values in each group and the actual value to be imputed for each group.

Using the assumption that 90% of the participants will actually be seen at the 36-month visit, the following table presents the power to detect differences in average change in LDL-C for the secondary analysis (i.e., analysis of participants with a 36-month lipid value):

Let $z_{\alpha} = 1.96$ for a two-sided test at $\alpha = 0.05$. Thus, DISC will have the following power to detect differences in average change in LDL-C at 36-months for the primary analysis (i.e., intent to treat analysis):

Difference in Average Change in LDL-C (mg/dl)	Power		
	Over- all	Males	Females
1.0	0.11	0.07	0.08
2.0	0.31	0.18	0.19
3.0	0.60	0.35	0.38
4.0	0.84	0.56	0.59
5.0	0.96	0.74	0.78
6.0	0.99	0.88	0.91

The powers listed in this table are probably reasonable estimates of the powers to detect a difference in average change in LDL-C when imputation is used. The imputation procedure would impute a number of identical values which, when combined with the observed LDL-C values, would decrease the variance of the observed LDL-C measures to some extent, depending on the number of values imputed. This would be countered by mean values for the two groups which would not have as large a difference as the difference in the observed LDL-C. The actual effect on the power to detect a difference in LDL-C changes will depend on the number of imputed values in each group and the actual value to be imputed for each group.

Using the assumption that 90% of the participants will actually be seen at the 36-month visit, the following table presents the power to detect differences in average change in LDL-C for the secondary analysis (i.e., analysis of participants with a 36-month lipid value):

Difference in Average Change in LDL-C (mg/dl)	Power		
	Overall	Males	Females
1.0	0.10	0.07	0.08
2.0	0.29	0.17	0.18
3.0	0.56	0.32	0.35
4.0	0.80	0.51	0.55
5.0	0.94	0.70	0.74
6.0	0.99	0.85	0.88

15.2.4 Analysis of Research Questions

General Analysis Strategies

In general, for the comparison between treatment groups of mean levels of an outcome of interest, ANCOVA provides a more powerful test than does a test of difference in mean change scores⁴. Moreover, the ANCOVA model may be readily rewritten using change scores as the dependent variable and, consequently, changing the slope for the baseline value⁵. Because change scores are likely to be easier for clinicians to interpret, this latter procedure will be used extensively in these analyses.

One of the problems with ANCOVA is that it requires the assumption that the observations come from a normally distributed population with constant variance. For those variables where this may not be true, normalizing or variance-stabilizing transformations, such as a log or square root transformation, will be considered.

ANCOVA models look primarily at the difference between treatment groups at defined points in time; for example, the analysis of LDL-C levels at 36 months. However, several of the research questions in this study are concerned with assessing the impact of one variable on another at sequential points in time. This type of analysis can best

be handled using repeated measures models for continuous or discrete variables⁶ to test, for example, the effect of dietary intervention on sexual maturation through adolescence.

Traditional repeated measures analysis of variance requires balanced (complete) data at each visit and have difficulty incorporating time-dependent predictors. Recently, there have been several approaches put forth which circumvent this problem. A two-stage random effects model^{7,8} can be used. This model assumes that probability distribution for the outcome is the same for each participant, but that a number of parameters ('random effects') vary across the participants. Liang and Zeger⁹, using a quasi-likelihood approach to avoid parametric assumptions about within-subject correlation, have proposed a family of generalized regression models for continuous or discrete data. For these analyses, a SAS/IML program developed at Johns Hopkins (GEE) will be used.

Specific Analysis Strategies

Using these basic approaches, brief descriptions of approaches to the analysis of the specific research questions of DISC 36 month data are described below.

Determine the effect of the fat-modified diet on LDL-C (primary efficacy outcome) and Total Cholesterol (secondary efficacy outcome) at 36 months

The primary analysis for efficacy will use an ANCOVA model with change in LDL-C level (baseline to 36 months) as the dependent variable and baseline LDL-C, treatment and gender and treatment-gender interaction as the independent variables. The initial analysis will include all participants with imputed values for those

participants who did not have a blood draw at the 36-month visit.

Subsequent analyses will include only those participants who had a 36-month LDL-C value. Secondary analyses will include terms for Tanner stage and changes in physical activity levels at 36 months.

For female participants, a separate model will be constructed to assess the effect of the phase of menses at the time of the final blood draws. However, this analysis looks at the change only at one point in time. To assess the possibility of trends in LDL-C change over time as the level of intervention intensity changes, repeated measures models will be used, taking into account the 12-month LDL-C level.

Other analyses of interest will investigate the prediction of the effect of dietary changes on the total cholesterol level by the Keys⁹ formula. This will be done using changes from baseline to the 36-month visit for total cholesterol and for the dietary data.

Short-term changes can be investigated using data on changes from baseline to the 12-month visit.

15.2.4.1 Primary Safety Outcome Measure

Definition

The primary safety outcome is change in height from baseline to the 36-month visit. To test for differences in the safety outcome we propose a one-sided test, at $\alpha=0.05$, of $H_0: HT_{UC} \leq HT_I$ versus $H_A: HT_{UC} > HT_I$, where HT_{UC} and HT_I are, respectively, the mean change in height in the usual care and intervention groups. The use of a one-sided test is justified in this case because only a failure of the intervention group to achieve full adult height would be considered an adverse

outcome. Another primary safety outcome is serum ferritin. This outcome will also be tested with a one-sided test.

Analysis of the primary safety outcome measures will also be by 'intention to treat', as specified for the primary efficacy outcome measures.

Imputation Procedures

For the DISC participants for whom a 36-month height measurement is not obtained, measurements made at previous visits may provide a good basis for imputing height at the 36-month visit. The participant's height at the 36-month visit will be estimated as the mean for the participant's treatment group plus the participant's observed average deviation from the gender-treatment group mean at earlier ages. In cases where the participant has not been seen since baseline, the gender-treatment group mean for the 36-month height will be imputed.

For serum ferritin, the imputation approach will be to impute the age-gender specific mean of the treatment group opposite that to which the participant was originally assigned.

Use of Data Collected Outside of the Visit Window

Height data which was collected outside of a visit window can still be utilized as described in Section A.4.

Power to Detect Differences in Height

The following table presents the observed values used to calculate the power for detecting various differences in height between treatment groups.

	Overall	Male	Female
No. Intervention	334	179	155
No. Usual Care	329	183	146
Baseline S.D.	6.9	6.4	6.1

MN36 S.D.	8.0	8.1	7.0
Correlation	0.89	0.87	0.90

Let $z_{\alpha} = 1.645$ for a one-sided test at $\alpha = 0.05$. Then DISC will have the following power to detect differences in average change in height for the primary analysis (i.e., intention to treat):

Difference in Average Change in Height (cm)	Power		
	Over- all	Males	Females
0.25	0.14	0.09	0.11
0.50	0.42	0.22	0.29
0.75	0.75	0.42	0.57
1.00	0.94	0.65	0.81
1.50	0.99	0.94	0.99
2.00	0.99	0.99	0.99

It is not known what impact the imputation procedure would have on the power to detect a difference in height since each participant with a missing height measurement would have an imputed value based on the mean of the treatment group plus the participant's average observed deviation from the mean from previous visits.

Using the assumption that 90% of the participants will actually be seen at the 36-month visit, the following table presents the power to detect differences in average change in height for the secondary analysis (i.e., analysis of participants with a 36-month height measurement):

Difference in Average Change in Height (cm)	Power		
	Overall	Males	Females
0.25	0.13	0.08	0.10
0.50	0.39	0.20	0.27
0.75	0.71	0.39	0.52
1.00	0.92	0.61	0.77
1.50	0.99	0.92	0.98
2.00	0.99	0.99	0.99

Power to Detect Differences in Serum Ferritin

The following table presents the observed values used to calculate the power for detecting various differences in height between treatment groups.

	Overall	Male	Female
No. Intervention	334	179	155
No. Usual Care	329	183	146
Baseline S.D.	20.2	22.0	17.6
MN36 S.D.	21.8	23.5	18.3
Correlation	0.58	0.57	0.51

Let $z_{\alpha} = 1.645$ for a one-sided test at $\alpha = 0.05$. Then DISC will have the following power to detect differences in average change in serum ferritin for the primary analysis (i.e., intention to treat):

Difference in Average Change in Serum Ferritin (ng/ml)	Power		
	Over- all	Males	Females
1.0	0.10	0.07	0.07
2.0	0.27	0.14	0.16
3.0	0.51	0.27	0.31
4.0	0.76	0.44	0.50
5.0	0.92	0.61	0.68
6.0	0.98	0.77	0.83

As with LDL-C, the imputation procedure would impute a number of identical values. The actual effect on the power to detect a difference in the serum ferritin changes will depend on the number of imputed values in each group and the actual value to be imputed for each group.

Using the assumption that 90% of the participants will actually be seen at the 36-month visit, the following table presents the power to detect differences in average change in serum ferritin for the secondary analysis (i.e., analysis of participants with a 36-month serum ferritin determination):

Difference in Average Change in Serum Ferritin (ng/ml)	Power		
	Overall	Males	Females
1.0	0.09	0.06	0.07
2.0	0.24	0.13	0.15
3.0	0.48	0.25	0.28
4.0	0.72	0.40	0.46
5.0	0.89	0.57	0.64
6.0	0.97	0.73	0.79

Specific Analysis Strategies

Assessment of impact of dietary intervention on attained height (primary safety outcome)

The ANCOVA model will use change in height (baseline to 36 months) as the dependent variable and baseline height, treatment group, baseline age and Tanner stage at 36 months as independent variables. Because males and females are known to have different growth patterns, this model will be run separately for the two genders. The primary analysis will be the intention to treat analysis with all participants included. Any participant who was not seen for the 36-month visit will have a height measurement imputed according to the procedures outlined above. Further analyses will include other explanatory variables such as change in dietary intakes (e.g., total calories, total fat, saturated fat, etc.). To look at change in height over time, a repeated measures analysis will be performed using data for height and the explanatory variables for the 6-month, 12-month and 24-month visit in addition to the data for the 36-month visit.

Assessment of impact of dietary intervention on serum ferritin (primary safety outcome)

The ANCOVA model will use change in serum ferritin levels (baseline to 36 months) as the dependent variable and baseline levels, treatment group, baseline age and Tanner stage at 36 months as independent variables. Because males and females are known to have different serum ferritin levels (especially after the initiation of puberty), this model will be run separately for the two genders. The primary analysis will be the intention to treat analysis with all participants included. Any participant who was not seen for the 36-month visit will have a serum ferritin level imputed according to the procedures outlined above. Because serum ferritin determinations were only done at baseline, at the 12-month visit and at the 36-month visit, repeated measures analysis will probably not be very revealing.

15.2.4.2 Secondary Outcome Measures

Secondary efficacy outcomes are change from baseline to 12 months in LDL-C and changes from baseline to 12 and 36 months in total cholesterol. Secondary safety outcomes are changes from baseline to 36 months in serum levels of zinc, folate, retinol and albumin, LDL-C/HDL-C ratio, measures of cognitive development (Woodcock-Johnson Math and Reading Clusters) and child behavior (Achenbach Child Behavior Checklist). An additional secondary safety outcome is the rate of sexual maturation, assessed at 12, 24 and 36 months. Imputation will not be used for missing data for the secondary outcomes.

Analysis of Research Questions for Secondary Outcomes

Determine the feasibility of maintaining a dietary intervention in adolescents

Two analysis approaches will be taken. First, the ANCOVA models will use the changes in the various nutrients measured at the 36-month visit, such as total calories, total fat, saturated fat and cholesterol as the dependent variable with baseline nutrient levels, gender and treatment group as independent variables. Second, a repeated measures model will be used. Such models, using the change in the nutrient levels between visits, will incorporate values from each visit of, for example, age, gender, Tanner stage and body mass index. An overall test of the treatment group difference will combine the information from the separate visits. An additional analysis of interest will be to use percent of RDA (or even a binary indicator for reaching the RDA) for each participant as the dependent variable in place of the nutrient levels discussed above.

Determine the long-term effect of the dietary intervention on psychosocial development, cognitive development and behavior in adolescents

Because the scores from psychosocial instruments are not necessarily additive, the appropriate analysis of model would use the score at the 36-month visit as the dependent variable and the treatment group, gender and baseline score as the independent variables. The norms for these instruments are age-specific. Accordingly, treatment groups will be compared in separate analyses of each visit at which the tests are administered (i.e., baseline, 12

months and 36 months), rather than using a repeated measures analysis.

Determine the long-term effect of the dietary intervention on other nutritional measures

The ANCOVA model will use change in the various measures (i.e., serum ferritin, serum zinc, albumin, folate and retinol) as the dependent variable with treatment group, gender and age and the baseline value of the nutrient of interest as the explanatory variables. Certain of these, such as serum ferritin, might be effected by menses. A separate analysis will be performed for female participants in which a term for the phase of the menses cycle at the point of the blood draw at the 36-month visit would be included in the model. Secondary analyses will use a logistic regression model to analyze the proportion of participants in each treatment group outside of a clinical 'normal' range for each measure.

Assess the long-term impact of the DISC diet on LDL-C/HDL-C ratio

The approach to this analysis will be similar to that outlined above for lipid levels.

Assess the long-term effect of the intervention on the rate of biological maturation

The repeated measures models will be appropriate for this analysis. In particular, the Liang and Zeger⁶ method is applicable to discrete data. In this case, Tanner stage will be the discrete dependent variable with treatment group and age as the independent

variables. Separate models for the two genders will be constructed.

Determine the effect of the dietary intervention on lipoprotein levels at various sexual maturation phases

A repeated measures model will be used for this analysis with separate models for the two genders. Included in the model will be the lipid measurement at each visit as the dependent variable with treatment group, age, Tanner stage and their interaction terms as the independent variables. For female participants, the hormonal assay data and menses data will be included as other explanatory variables in the model, using the levels of the sex hormones and menses cycle data, collected for the specific clinic visit. A similar model for male participants will also be constructed since sex hormones are also being measured for them.

Determine the effect of the dietary intervention on the incidence of other cardiovascular disease risk factors

The analysis for this question will use ANCOVA models for continuous response variables and logistic regression for binary variables, such as smoking or high blood pressure. Because these factors appear over a period of time, repeated measures models will be used to identify time-dependent factors which might be related to the appearance of the risk factors. The models will be constructed with the risk factors as the dependent variables and treatment, gender and levels of nutrient intake as the explanatory variables. The Liang and Zeger models⁶ can properly analyze the

repeated measures of both continuous and binary variables and will be used here.

Determine the effect of the dietary intervention on sex hormones in both male and female participants

ANCOVA models will be appropriate for the sex hormone data collected as part of the NCI-funded ancillary study. The actual sex hormone levels at 36 months will be the dependent variable with treatment group as the independent variable. Baseline values are available on only a small subset of the participants due to the late start of this ancillary study and so cannot be used in the model. Separate models will be built for male and female participants. For female participants, the phase of the menstrual cycle will also be included as an explanatory variable. Additional explanatory variables will include nutrient intake levels, achievement of DISC dietary goals and LDL-C levels. These variables will also be included in a repeated measures analysis of the hormone data.

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15.3 QUALITY ASSESSMENT

The data on performance of the Clinical Centers with respect to participant recruitment and follow-up, completeness of data, etc., will consist primarily of simple tabulations of counts and percentages. During participant recruitment, each Clinical Center will be kept informed of the characteristics of the treatment groups and whether the intervention and control groups of each Clinic are comparable. This will be done by comparing the percentage of the intervention group and the percentage of the control group having each characteristic (for characteristics with discrete values) or by comparing measures of central tendency for the characteristic in the intervention group and

in the control group (for characteristics with a continuous distribution of values).

The data from the split duplicate analyses by the Central Laboratory will be paired together and the differences computed so that the following can be calculated for each laboratory test:

1. The mean of the 2n determinations.
2. The between-sample standard deviation of the n pairs of determinations.
3. The mean absolute difference of the n pairs.
4. The average error (100 times the ratio of the mean absolute difference to the mean of the 2n determinations).
5. The coefficient of variation (100 times the ratio of the standard deviation to the mean of the 2n determinations).

These results will be used to determine how the within-person variability is increased by measurement error in the biochemical determinations. If the measurement error of a particular biochemical determination is so large that it increases the within-person standard deviation substantially, this will have a substantial impact on significance tests or confidence intervals computed for this variable.

In this case, multiple analyses of this determinant and use the mean (or some other measure of central tendency) of the determinations used to reduce the measurement error.

Analysis of the quality assessment data for secular trends in biochemical testing will require the repeated submission of specimens from a donor pool. Specimens will be submitted at intervals throughout the study and results compared to identify any trends over time. The analysis will use a multiple regression model containing a term for each time period, representing the amount of change in the value of the

specimen due to secular trends in the laboratory determinations for that period, and a term for each time period representing the amount of change in the value of the specimen due to deterioration of the frozen sample for that period.

Analyses of the quality assessment data for food recall coding will be similar to those described above for technical error of laboratory determinations and will also include (for each nutrient and each coder) scatter diagrams of the values based on the two independent codings of the food recalls.

CHAPTER 16

ORGANIZATIONAL STRUCTURE

16.1 Introduction

DISC will be divided into the following phases: An 8-month planning and Protocol development period, a 16-month feasibility study, a 3-year full-scale trial (DISC I), a seven-year extension of full scale follow-up (DISC II), and a 12-month closeout and final data analysis period. The organizational structures planned for DISC I and II are described in the sections below.

16.2 NHLBI Project Office

DISC I and II will be supported by research cooperative agreements from the National Heart, Lung, and Blood Institute (NHLBI). NHLBI Project Office staff in the Prevention Scientific Research Group will work closely with the DISC Coordinating Center staff and the staff of participating Clinical Centers to provide necessary scientific collaboration to assure the quality of the work to be performed under the provisions of the awards from the NHLBI. An NHLBI biostatistician will be part of the Project Office and will work with the Steering Committee on design and analysis issues. The grants management officer will work closely with the project officer in order to handle the financial aspects of DISC.

The NHLBI Project Office will serve as a direct link from the organization of DISC to the Director of the NHLBI to channel inquiries, recommendations and policy directives.

16.3 Clinical Centers

The six DISC Clinical Centers will be:

1. Johns Hopkins University - Baltimore, MD.
2. Northwestern University Medical School - Chicago, IL.
3. University of Iowa - Iowa City, IA.
4. New Jersey Medical School - Newark, NJ.
5. Louisiana State University/Children's Hospital - New Orleans, LA.
6. Kaiser Permanente Center for Health Research - Portland, OR.

The role of the Clinical Centers will include the following functions:

1. Developing the study Protocol, Manual of Operations, and data forms in collaboration with other study investigators.
2. Implementing the approved Protocol at each Clinical Center by identifying and enrolling approximately 20 children aged 8-10 years into the feasibility study and approximately 80 into the full-scale study. Parents or guardians of the children will also be enrolled.
3. Performing the specified nutrition education and intervention for the assigned treatment group.
4. Conducting baseline and follow-up examinations of the study population.
5. Collecting, editing, and sending data obtained in accordance with the Protocol and Manual of Operations to the Coordinating Center. Working with the Coordinating Center to maintain the quality of the data collected.
6. Evaluating the progress of their clinic in carrying out the protocol and alerting the Coordinating Center and Steering Committee to major problems.

7. Preparing publications of study results in collaboration with other investigators and NHLBI staff.

16.4 Coordinating Center

The Coordinating Center will be located at Maryland Medical Research Institute, Baltimore, MD. The Coordinating Center will be responsible for the following tasks:

1. Developing the study Protocol, Manual of Operations, and data forms in collaboration with the other study investigators.
2. Developing, pretesting, implementing, and maintaining the database management system.
3. Coordinating training, certification, and recertification of clinical center staff in examination and data collection processes.
4. Designing and implementing a random allocation program to issue treatment assignments with essential safeguards.
5. Contracting with and monitoring a Central Laboratory for the analysis of blood samples and a Nutrition Coding Center for nutrient composition coding of 24-hour dietary recalls. Pretesting and coordinating the collection of laboratory results and 24-hour dietary recall coding and integrating these into the main database.
6. Carrying out quality assurance procedures in conjunction with clinical centers. Maintaining audit trails on data entry, reviewing adherence to schedules, and verifying completeness of data collection, and notifying Clinics of error rates and deficiencies. Cooperating with other investigators in obtaining inter- and intra-observer reliability measures for

questionnaires and procedures so that information can be incorporated in analyses.

7. Assisting in the planning, organization and conduct of study meetings, writing and distributing minutes. Preparing periodic progress and quality control reports.
8. Providing support for the forms development and approval process.
9. Providing leadership for the analysis of study data in collaboration with the Steering Committee and NHLBI Project Office.
10. Delivering data to clinical centers for specific analyses as directed by the Steering Committee and Project Office.
11. Assisting in the organization and conduct of site visits to each clinical center in conjunction with NHLBI and the working groups to insure compliance with the provisions of the Protocol and Manual of Operations.
12. Notifying principal investigators of any special local problems in performance, or the project officer if a timely resolution of the problem is not possible.

16.5 Central Clinical Laboratories

The Central Lipoprotein Laboratory will be located at Johns Hopkins Hospital, Baltimore, MD. This Laboratory will be responsible for training and certifying Clinical Center personnel in collection, preparation, and shipment of blood specimens and for performing determinations of total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol (by formula), apolipoprotein A-1, and LDL apolipoprotein B.

Two other Central Laboratories will perform biochemical tests on blood specimens from DISC participants in the main study. The Johns Hopkins Hospital Clinical Laboratory will be responsible for carrying out a standard chemistry panel with 13 component tests including albumin, SGPT, alkaline phosphatase, and others, plus T4. The Nutritional Biochemistry Laboratory of the Centers for Disease Control, Atlanta, GA will be responsible for performing determinations of cholesterol ester linoleate:oleate ratio and the following micronutrients: ferritin, zinc, copper, folate, retinol, tocopherol, and carotenoids. Endocrine Sciences, Calabases Hills, Calif., will perform hormone analyses for the Hormone Study (see Chapter 10 for details). In DISC II, the Lipid Research Unit of the Johns Hopkins Hospital, Baltimore, MD, will carry out DNA analyses for the DNA Ancillary Study (see Chapter 20 for details). The Central Lipoprotein Laboratory will serve as the recipient of all specimens from the Clinical Centers and will be the distribution center for specimens sent on to the two non-lipid laboratories, the laboratory performing hormone analyses, and laboratories involved in ancillary investigations.

16.6 Nutrition Coordinating Center

The Nutrition Coordinating Center will be located at the Nutrition Coordinating Center of the University of Minnesota, Minneapolis, MN. This Center will be responsible for training and certifying Clinical Center personnel in the collection of 24-hour dietary recall data, and for coding and nutrient analysis of the 24-hour dietary recall data.

16.7 DISC I Committees and Working Groups

16.7.1 Steering Committee

The Steering Committee (SC) will be made up of one voting member (the principal investigator) from each of the six Clinical Centers, the Coordinating Center, and the Project Office, along with the study vice-chairperson. A National Cancer Institute representative will be included as a non-voting member of the SC. If a vote is taken, passage will require a two-thirds majority of the non-abstention votes. If the principal investigator of a study center is absent, that person's vote may be delegated to another member of that center.

The Steering Committee will meet regularly to review study progress. It will provide overall scientific direction for the study through consideration of recommendations from the working groups and others. The Steering Committee will guide the development of the study Protocol, Manual of Operations and data forms, reviewing and approving major changes. It will review and approve ancillary studies, provide advice and assistance to all centers and NHLBI on operational matters, and resolve problems submitted by any center involved in the study. The Steering Committee will review the results of the feasibility study and approve the start of the full-scale trial. It will also monitor the performance of Clinical Centers through site visits. Minutes of Steering Committee meetings will be taken, prepared and distributed by Coordinating Center staff.

A Publications Subcommittee will be responsible to the Steering Committee and will review and approve proposals and drafts for manuscripts and presentations. This subcommittee will also monitor progress on manuscripts.

16.7.2 Working Groups for DISC I

Several DISC special area working groups will be established by the Steering Committee to take responsibility for study activities within their area of expertise such as selection and/or development of data forms and writing and revising assigned sections of the DISC Protocol and Manual of Operations as well as training, certification and re-certification in specific areas. Each working group will be composed of one or more representatives from each Clinical Center, the Coordinating Center, and the NHLBI Project Office. The working groups are listed below along with the specific role and area of concern of each.

1. The Design and Analysis Working Group will oversee the formulation of hypotheses, the specification of study outcome variables, definitions of key terms, and other aspects of overall study design and analysis.

2. The Eligibility and Recruitment Working Group will prepare the participant eligibility criteria and deals with problems of participant recruitment and retention.

3. The Intervention Working Group will recommend methods of intervention for the intervention and control groups. It will develop the overall plan and materials for implementing and maintaining the interventions, including schedules and context of visits. Special subgroups composed of behaviorists and child group leaders will report to the Intervention Working Group on topics within each area.

4. The Data Collections and Quality Assurance Working Group will define the database variables, specify the method of measurement and frequency of collection of each variable and monitor the quality of

data collection. This group will be made up of three subgroups which are listed below.

5. The Dietary Assessment Working Subgroup will be concerned with the assessment methods for dietary intake, food patterns, and nutrition knowledge and attitudes.

6. The Clinical and Psychosocial Assessments Working Subgroup will be concerned with clinical and anthropometric measurements, medical history, family history and the smoking and medication histories. It will also deal with the areas of demographic measures, family dynamics and support, psychosocial measures in children and adults, and family behavior.

7. The Biochemical Working Subgroup will be concerned with the assessment of biochemical maturation, lipid/lipoprotein and other biochemical determinations.

16.7.3 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee will be a body external to DISC -- not directly involved in the DISC -- and consist of experts in the areas of biostatistics, epidemiology, clinical medicine, pediatrics, behavioral intervention, clinical trial methodology, and nutrition. It will be appointed by NHLBI, with consultation from the Steering Committee, to provide an independent review of the DISC data and will meet approximately twice each year. This Committee will review the protocol, the treatment effect data, the quality control data, and the data on performance of the study units, and will make recommendations to the NHLBI Project Office and to the DISC Steering Committee for modifying study procedures to improve performance or

quality, and for further data analyses to help explicate the study research questions.

Each meeting of this Committee will be attended by at least one representative from the Coordinating Center (including the principal investigator or his designate), the chairperson and/or vice-chairperson of the Steering Committee, representatives from the Project Office (including the project officer), and other Clinical Center principal investigators, as appropriate.

16.8 Revised Committee Structure for DISC II

DISC II, as an extended follow-up of DISC I, will focus mainly on the maintenance of participation, on data collection with special attention to endpoint data, on analyses, and on the publication of manuscripts. The following changes in committee structure will be implemented in DISC II to serve these new functions.

16.8.1 Revised Committees

Steering Committee

An existing committee. Principal Investigators from all sites, Project Officers, and designated others will provide study leadership.

Operations Committee

A revised committee which will be a subcommittee of the Steering Committee. Its new role is to implement Steering Committee decisions, expedite the conduct of the trial, and deal with internal problems.

Publications Committee

An existing committee which reviews and approves proposals for publications, keeps track of publication status, and facilitates the publication process.

Design and Analysis Committee

Previously, the Design and Analysis Working Group. It will provide study design and statistical analysis leadership.

Quality Assurance Committee

An existing committee which will assure the quality of study data and will review the training and certification process.

Clinical Monitoring Committee

A revised committee that was previously the Growth Monitoring Committee. Its new role will include all aspects of safety monitoring (identification of individual subjects for followup). This should be done centrally by the Coordinating Center, what should be done locally by the clinical centers, and obtain and review safety monitoring results.

Cohort Maintenance Committee

Previously the Eligibility and Recruitment Working Group. The name change reflects that DISC II subjects will already be identified.

Intervention Committee

Previously Intervention Working Group which will develop intervention and maintenance approaches and content.

16.8.2 Revised Working Groups

Dietary and Micronutrient Assessment Working Group

Previously the Dietary Assessment Working Group which will now include both dietary intake and serum micronutrient assessment.

Biochemical Assessment Working Group

Now will take responsibilities for all blood chemistries including chemistry panels and hormone analyses, but not micronutrients.

Clinical and Psychosocial Assessment Working Group

An existing working group which will include psychosocial and clinical measurements.

Behavior Assessment Working Group

New working group which will address smoking and physical activity measurement and any other behavior measurements that will be needed.

16.8.3 Other Working Groups

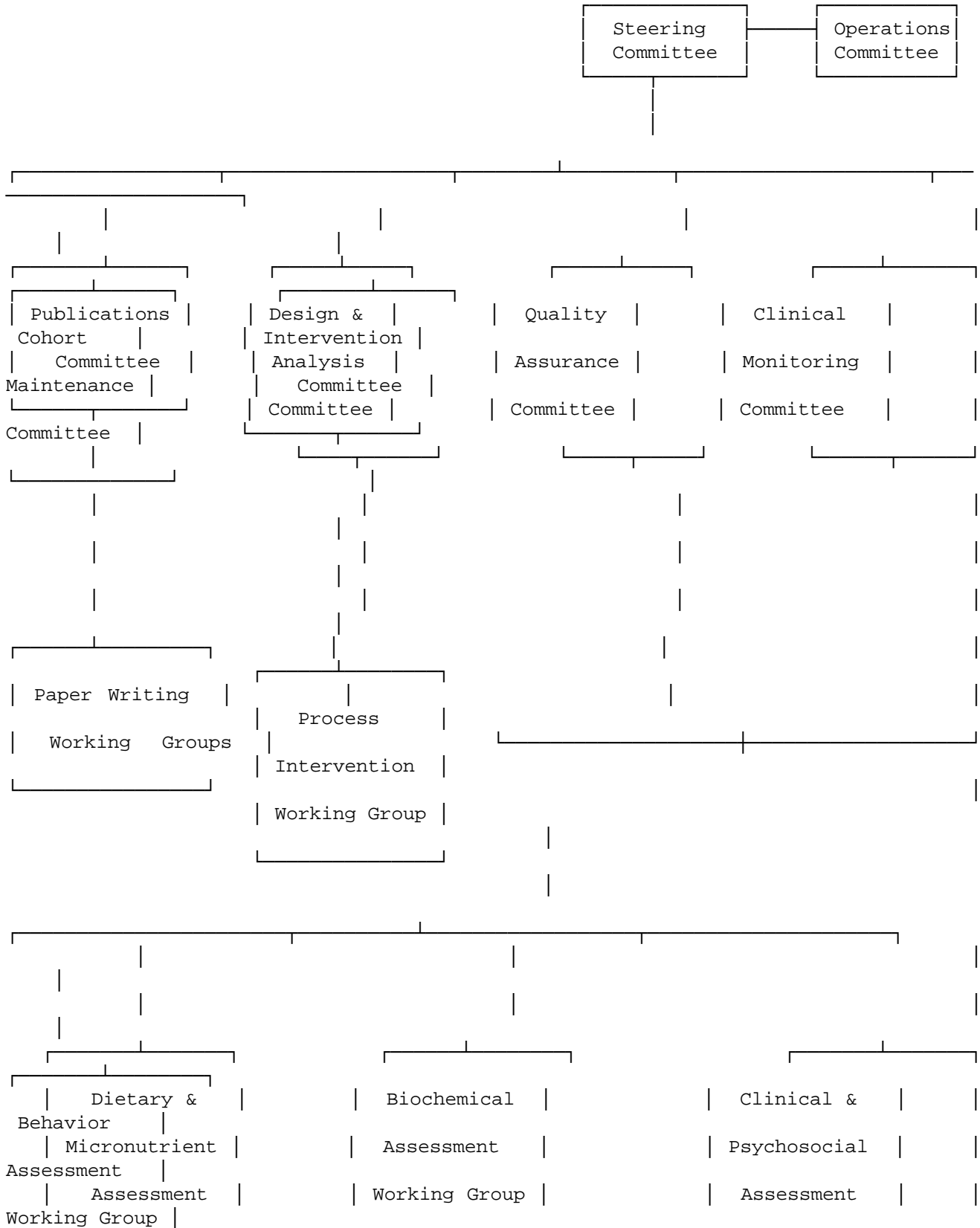
Paper Writing Working Groups

Existing and proposed writing groups will write and submit manuscripts.

Process Intervention Working Group

Previously the DISC Child Group Leaders Group which will be renamed because the subjects will no longer be children.

Committee Structure for DISC II



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CHAPTER 17

PUBLICATIONS AND PRESENTATIONS

17.1 EDITORIAL POLICY OBJECTIVES

The editorial policy objectives of the Publications Committee (Publications and Presentations Committee) will be:

17.1.2 To insure and expedite timely presentation to the scientific community of data resulting from the DISC trial;

17.1.3 To critically review each manuscript to insure scientific merit and accuracy;

17.1.4 To insure that press releases, interviews, presentations, and publications of DISC materials are accurate and objective, and do not compromise the collaborative nature of the trial or the acceptance of its results;

17.1.5 To encourage all investigators, particularly those of junior faculty rank and those in other health professions, have the opportunity to participate in the presentation of DISC papers;

17.1.6 To establish procedures that allow the DISC Steering Committee and the NHLBI to exercise final review responsibility for all publications and presentations;

17.1.7 To insure that membership in writing committees for DISC papers reflects active participation in various phases of manuscript preparation, such as data analysis and interpretation of the results, as well as writing.

17.1.8 To develop and update a complete list of all DISC presentations and publications and to distribute regular updated lists to all DISC investigators.

17.2 DEFINITIONS

17.2.1 Final Papers and Presentations

Final papers and presentations are those reporting results dealing with the main hypotheses (primary and secondary outcome measures) of the randomized controlled trial.

17.2.2 Mainstream Papers and Presentations

Mainstream papers and presentations are all other papers reporting results of the national collaborative trial and its common data set.

17.2.3 Other Papers and Presentations

Other papers and presentations are those not included in the above two categories.

They include work done in ancillary studies by a subset of DISC centers or by a single center. They also include papers reporting local data from a single center.

17.3 GENERAL STATEMENT OF POLICY

To minimize the possibility that published materials may be based on faulty data, it is the policy of the DISC Publications Committee that all definitions and data considered for final, mainstream, substudy, ancillary or local papers, be submitted to the Publications Committee for review by the Coordinating Center to verify that they are accurate and consistent with data and definitions used in other DISC documents. The Publications Committee has the responsibility to promptly submit suggested outlines of all papers to the Coordinating Center for review. The Publications Committee also has the responsibility to promptly submit final drafts of all papers to the Coordinating Center for review for accuracy and consistency of the data presented. Final drafts of papers will be circulated to all DISC Principal Investigators for their review and comments to the Publications Committee.

A goal of editorial policy is that the selection of writing committee members

be equitable and fair to all groups and individuals participating in the DISC collaborative program. Consideration will be given to the exceptional efforts of groups or individuals with particular attention to the encouragement of participation by junior colleagues.

Local DISC centers are permitted and encouraged to write papers on local data and experience. A local paper dealing with a mainstream topic should be prepared only after the broader mainstream paper, based on the national trial, has been published or officially accepted for publication.

The Publications Committee is charged with the task of periodic review of the work of all writing committees, aiding and encouraging them and revising their membership when indicated (with written notification and right of appeal).

17.4 PROCEDURES

17.4.1 Final and Mainstream Papers and Presentations

17.4.1.1 Identification of the Final and Mainstream Papers

At regular intervals, the Publications Committee will distribute to all DISC centers titles of final or mainstream papers. These papers will be identified by the DISC Publications Committee based on suggestions received from members of participating centers and other groups of writing committees. They must use data collected by all centers and will be subject to final approval by the Steering Committee. If a writing committee decides that its paper topic is too broad and should be divided into two or more papers, the writing committee Chair is responsible for communicating with the Chair of the Publications Committee explaining the writing committee's recommendation for the division of the final or mainstream paper into two or more components. The writing committee should identify which of the components it recommends as its responsibility, and suggest titles and outlines for other components. The Publications Committee will consider these recommendations and, when appropriate, redefine the charge to the existing writing committee. Any additional final or mainstream papers will be specified,

and will also be subject to the above specified Policy Procedures.

If any writing committee identifies other topics or titles for final or mainstream papers, either directly or indirectly related to the charge of that writing committee, the Chair of the committee will communicate these topics to the Chair of the Publications Committee. The policies and procedures specified above will apply.

17.4.1.2 Selection of Writing Committee Members and Chairs

For each paper identified, an ad-hoc committee of volunteers from all centers will be appointed and charged with the responsibility of writing the paper in a prescribed format and within a stated time limit. In general, the steps listed in Section 17.4.2.2 will apply for final and mainstream papers. The policies of equitability, encouragement of participation by junior colleagues, and recognition of exceptional contributions will apply to final and main papers, and to all other DISC publications and presentations.

17.4.1.3 Authorships and Credit

The main "author" of final papers and presentations will be the DISC Research Group. For mainstream papers and presentations, writing committee names will be listed as authors on behalf of the DISC Research Group. The Chair of the writing committee, with the concurrence of other members, will determine the order of authorship. A major criterion for this determination will be the effort and contribution of writing committee members in the preparation of the manuscript.

A credit list of all major DISC committees, units, and centers with their members is to appear in each final and mainstream paper, printed as a footnote at the end of the manuscript.

17.4.1.4 Requests for Reprints

Requests for reprints of final and mainstream papers are to be directed to the DISC Coordinating Center.

17.4.2 Papers and Presentations Other than the Final and Mainstream Papers

17.4.2.1 Identification of Topics or Selection of Titles

Members of DISC Centers who identify additional final or mainstream papers which draw on data collection by all centers, will communicate the topic or title of the paper they wish to have considered for publication to the Chair of the Publications Committee. Other papers and presentations developed based on special data sets for substudies or ancillary studies will be identified by the Publications Committee.

17.4.2.2 Selection and Composition of Writing Committees

As soon as mainstream or other papers are identified and approved by the Publications Committee, the Chair of the Committee will communicate with all centers requesting nominees to participate as members of a writing committee for that paper. A specified date (deadline) for submission of nominations will be included.

The Publications Committee will select from the submitted list of nominees the membership of the writing committee for that paper. A convener of the writing committee will be identified so that work may begin as soon as possible.

The Chair of the Publications Committee will notify the Convener of the writing committee and other committee members requesting that the Convener initiate steps for appropriate selection of a Chair of the writing committee. No specific guidelines for this democratic election will be provided. The method will be at the discretion of the Committee members. One approach which has been used is for a writing committee member who has waived election to assume responsibility for polling the other writing committee members. If the Publication Committee is aware that a member of a writing committee has waived election to Chair, then it will be appropriate to identify that individual as the Convener of the group.

As soon as the Chair is identified, it is his/her responsibility to communicate with other committee members to develop a detailed outline, to identify

data needed from the Coordinating Center, and to write the manuscript. To reach publication, one or more meetings of the writing committee may be necessary. Because of costs, it is recommended that such meetings be held to a minimum or be incorporated with other scheduled DISC or national scientific meetings.

For the writing committees of other papers (non-mainstream based on local data or data from less than six participating clinics), the members will be designated by the participating centers.

17.4.2.3 Preparation and Submission of Manuscripts

The following steps should be followed in the preparation of manuscripts. The Chair of the writing committee will:

- a. Contact each writing committee member to discuss the charge to the committee.
- b. Draft dummy tables which each member of the writing committee considers appropriate and needed for writing the manuscript. To facilitate the servicing of all DISC writing committees and the effective testing of hypotheses, initial requests for tables per paper will not exceed fifteen. Subsequent requests for additional tables can be made. Additional requests will be processed according to the priorities of the DISC Coordinating Center.
- c. All comments on the charge of the writing committee and copies of drafted dummy tables will be sent to the Chair of the writing committee.
- d. The Chair will collate comments and dummy tables and solicit opinions of the writing committee members. When a final decision is reached, the Chair will submit the dummy tables (or data requests) to the Coordinating Center with copies to the Chair of the Publications Committee.

- e. The first meeting of the writing committee will be after the Coordinating Center has produced the tables requested by the writing committee, and after they have been reviewed by writing group members. In this way, the first meeting will be more efficient and concerned with review of available data, modifications of tables, identification of other needed information, and not preliminary discussion on the charge to the committee. The Coordinating Center will identify conflicts in proposed dummy tables or data requests between two or more writing committees, and provide the writing committees involved with the conflicting dummy tables requested by other writing committees. If the conflict cannot be resolved by the Chairs of the writing committees, the issue will be resolved by the Publications Committee as the final arbitrator.
- f. Members of each DISC writing committee will participate actively in the writing and review of the paper assigned to that committee. Contributions from every member of the writing committee should be encouraged and required by all committees. The Chair will have the responsibility for obtaining contributions from every member of his/her committee. If any member of the writing committee does not respond to the chair's request or does not contribute to the writing of the paper, the Chair must take immediate action through the Publications Committee to determine the interest and intentions of the person involved. If there is no indication of interest, the Publications Committee will replace the individual.
- g. The Chair of each writing committee will approve the final version of the manuscript before its submission to the Publications Committee.
- h. If, in the judgement of the Publications Committee, a writing committee is not working well and there is an unjustifiable delay in writing the paper assigned, the Committee will change either the Chair or the entire membership in order to expedite the writing of the paper.

- i. For mainstream papers and presentations, names of members of the writing committee will be listed as authors on behalf of the DISC Cooperative Research Group. The Chair of the writing committee, with the agreement of other members, will determine the order of authorship. A major criterion for the determination will be the effort and contribution made by the members in the writing of the manuscript. The authorship of other non-mainstream papers will be designated in the usual manner for a scientific report, with the order of names appearing after the title to be determined by the participating center(s). The authorship of a local paper will be determined at the discretion of the Principal Investigator of the center. The Publications Committee will act as referee, if requested, to help decide the order of authors listed. In addition to the statement of authorship, a local paper will state clearly that the work was a substudy or ancillary study of DISC and will acknowledge grant support from NHLBI. At the end of the list of authors of the paper an asterisk will appear, footnoting that the work was performed as part of DISC, as a substudy, an ancillary study, or an analysis of local DISC data. Where appropriate, a listing of participating centers and participants who are not authors (generally with not more than three persons from each center) will be included. The decision on the composition of the listing will be made by participating centers and will be refereed by the Publications Committee.
- j. A credit list of all major committees, units, and DISC centers with their members (generally no more than three persons from each center) will appear in each final and mainstream paper, as a footnote at the end of the manuscript.
- k. Requests for reprints of final, mainstream, and substudy papers will be directed to the DISC Coordinating Center.
- l. The DISC Steering Committee will have the final authority to review and

approve all DISC papers for publication. The Chair of the Publications Committee will present the recommendations of the Publications Committee in a timely fashion. (Specific procedures for the Steering Committee review process will be developed later.)

m. The Chair of the Publications Committee will submit a final draft of each DISC manuscript to the Coordinating Center for final check on accuracy of the data. This will be done at the same time as the paper is submitted to the DISC Steering Committee for review.

n. The Coordinating Center will be asked to agree to a specified time limit for the review and response to the Chair of the Publications Committee.

o. It is intended that the procedures outlined above will enhance the initiative and productivity of DISC investigators in writing meaningful and relevant manuscripts.

p. Since not all circumstances causing disagreement among DISC investigators can be foreseen, the DISC Steering Committee, using recommendations of the Publications Committee, will be the final arbitrator of disputes concerning manuscripts.

17.4.3 Preparation and Submission of Abstracts for National and International Meetings

17.4.3.1 The DISC Publications Committee will maintain a current list of all relevant meetings and their deadlines for submission of abstracts. Abstracts for presentations are to be prepared when a manuscript on the same issue is in a final stage of preparation (final, mainstream, substudy, ancillary, or local manuscripts).

17.4.3.2 Abstracts of mainstream, final, substudy, local and ancillary study presentations must be approved by the Publications Committee before they are submitted to any national or international organizations. Abstracts submitted for review will be accompanied by copies of tables and any other data on which the text of the abstract is based, so that all

relevant data may be reviewed along with the abstract. The Coordinating Center will have a minimum of two weeks time for data analysis. Writing committees, or individuals submitting abstracts should be very selective in their data requests and only tables on the major topics of the abstract should be requested. Detailed tabulations dealing with special topics will be reserved for later preparation of the text for a presentation or of the manuscript for a publication. Generally, five or six tables will be sufficient for abstract preparation. On rare occasions, examination of these preliminary tables may result in one or two additional tables. The Coordinating Center will meet these additional requests on a timely basis, if possible. If there are several requests to the Coordinating Center for data analysis within a narrow span of time, the Chair of the Publications Committee will set priorities for data analysis. Abstracts which do not have accompanying related data will not be reviewed by the Publications Committee.

17.4.3.3 Any DISC investigator or group may prepare an abstract on a subject appropriate to DISC investigation. It may be based on a topic already assigned to a writing committee, if the person preparing the abstract is a member of that committee. The abstract may be on a new topic originating from any DISC investigator. All abstracts must be approved by:

- a. The DISC Writing Committee, if the abstract deals with the topic assigned to that committee;
- b. The DISC Publications Committee; and
- c. The DISC Steering Committee.

17.4.3.4 No abstract shall be submitted to any national or international organization for consideration without the prior approval of the DISC Publications Committee.

17.4.3.5 Since approval by the entire Steering Committee, prior to submission of an

abstract, may interfere with meeting submission deadlines, it is stipulated that:

- a. The abstract be approved by the Steering Committee within a minimum of two working days.
- b. Failure to reply within two working days by any Steering Committee member will be considered approval of the abstract by that member.
- c. The time limit for approval of an abstract will not exceed 2-3 weeks.
- d. If the DISC Steering Committee disapproves a submitted abstract, the author(s) will be required to withdraw that abstract immediately.

17.4.3.6 Approved DISC mainstream, final, and substudy abstracts will be presented to the DISC Principal Investigators for suggestions regarding presenters.

If responses are not received within two weeks, the Chair of the Publications Committee will make the selection. The presenter must be a member of the writing (ad-hoc) committee responsible for writing the mainstream, final, or substudy manuscript on behalf of the DISC Cooperative Research Group. The selection of the presenter of the abstract material at the meeting will be at the discretion of the manuscript writing committee or the Publications Committee (if a writing committee has not been formed). Regardless of which body selects and approves the presenter, the selection of a presenter must also be given final approval by the DISC Steering Committee.

17.4.3.7 If an abstract is prepared on a topic for which a writing committee has not been selected, the Publications Committee will select a writing committee as soon as the content of the abstract is approved. The DISC Coordinating Center will have a representative on this writing committee, as in all DISC writing committees, to expedite communication with the Coordinating Center and facilitate timely analysis of data and preparation of art work and slides for the presentation.

17.4.3.8 DISC writing committees for presentations are required to submit the

complete text and visual aids (including tables and graphs) of the presentation to the Publications Committee for review prior to the date of the meeting. If the complete text and visual aids for a presentation are not approved by the Publications Committee, the material will not be presented, even though its abstract may have been approved for presentation. Each presentation will have a sentence at the beginning identifying it as the work of the DISC Cooperative Group and stating that the material is being presented on behalf of the DISC Cooperative Research Group.

17.4.3.9 Slides used at meetings or for publications will be sent to DISC Principal Investigators by the Publications Committee. The Chair of the Committee, in collaboration with the presenter, will work closely with the Coordinating Center on which graphics should be produced as slides so that one standard set will be available for each final data set and for distribution to all DISC Centers.

17.4.3.10 The Chair of a writing committee for a presentation based on a local or ancillary study is responsible for the submission of the complete text and visual aids (including tables and graphs) of the presentation to the Publications Committee for review and approval prior to the date of the presentation. If the complete text and visual aids of a local or ancillary presentation are not approved by the Committee, that material will not be presented even though its abstract may have been approved for presentation.

17.4.3.11 Once mainstream, final, or substudy material has been presented at a scientific meeting, the tables used will be made available to DISC professional staff and may be used by them at other scientific meetings.

However, such subsequent presentations should not appear in published form unless the data from the original presentation have been published.

17.4.3.12 In the case of materials scheduled for presentation before organizations

issuing press releases, the presenter may submit the text of the presentation after it has been approved by the Publications Committee for release to the press. Such a release will be coordinated with the NHLBI Project Office. If the presentation is based on a manuscript not yet accepted for publication in a peer review journal, a sentence must be included on the front page of the release indicating the preliminary nature of the results.

17.4.4 Invitations to the DISC Investigators for Presentation of DISC Materials

The DISC Cooperative Research Group welcomes opportunities to participate and present reports at national and international scientific meetings. When an invitation is received by a member of the DISC Cooperative Research Group, DISC policies with regard to publications and presentations are to be followed.

17.4.4.1 When a personal invitation to a DISC investigator to make a presentation is received, notification of this invitation is to be sent to the Publications Committee for listing with all presentations on behalf of the DISC Research Group.

17.4.4.2 When an invitation involves more than one investigator or if it comes to the Chair of the Steering Committee or the Chair of the Publications Committee, then the Publications Committee will be notified in order to decide who will represent DISC.

17.4.4.3 All presentations in response to invitations will be based on published DISC materials unless approved beforehand by the Publications Committee and the Steering Committee.

17.4.4.4 Any presentation of unpublished DISC data must be reviewed and approved by the Publications Committee prior to the date of presentation.

17.4.4.5 Requests received by Principal Investigators or their staff, to present or discuss previously published DISC data at local meetings, need no prior clearance by the Publications Committee. DISC investigators are

encouraged to accept such invitations. It is requested that Principal Investigators receiving such invitations notify the Publications Committee so that it can keep records of these presentations. Any publication of such presentations or discussions must be approved by the Publications Committee before publication.

17.4.5 Use of DISC Materials for Graduate Student Theses

17.4.5.1 Requests for use of DISC data by students will be reviewed by the Publications Committee.

17.4.5.2 The student requesting DISC data must be associated with DISC. A DISC Principal Investigator must act as the student's "sponsor" with regard to the data request.

17.4.5.3 DISC data may not be used by students if it is related to a DISC mainstream or final paper which is in progress or if the Publications Committee deems the data necessary for a future mainstream or final paper.

17.4.5.4 If the Publications Committee recommends approval for the use of the requested data, a review committee will be established and will include the student as the convener of the committee.

17.4.5.5 The review committee will take no action regarding publication or presentation until the student has completed and defended the thesis, provided this occurs in a reasonable length of time. (The student's sponsor will report on the student's progress to the Publications Committee.)

17.4.5.6 The student must include the following in the completed thesis:

a. A statement acknowledging DISC for use of the data.

b. A statement indicating that the opinions, ideas, and interpretations included in the thesis are those of the student alone and not necessarily those of the DISC investigators.

17.4.5.7 When the thesis has been completed as determined by the sponsor, the review

committee will proceed to prepare the materials for publication.

17.4.5.8 The DISC publication policies will apply to any material published from the thesis.

17.4.5.9 DISC reserves the right to proceed with materials for publication on the thesis topic if, in the view of the Publications Committee and the student's sponsor, the student has not made reasonable progress on completing the thesis.

17.5 ADMINISTRATIVE PROCEDURES

1. The Publications Committee will hold interim meetings between regularly scheduled meetings of the DISC Steering Committee to:

a. Monitor the status of DISC publications and presentations;

b. Approve requests for new papers, presentations, publications or abstracts;

and

c. Formulate the content of reports to the Steering Committee on the status of DISC publications and presentations.

9/16/93

CHAPTER 18
POLICY MATTERS

18.1 Privacy of Records

Confidentiality of stored records will be maintained with implementation of the following policies:

1. All records will be kept by assigned I.D. numbers.
2. No personal identifiers of DISC participants will be sent to the Coordinating Center or any other study unit. Only I.D. number and six-letter code will be used to identify study participants on the data forms.
3. Clinical Centers will store the data forms in locked files and permit access only by authorized individuals.
4. Final results will be presented for review in conferences and journals in the form of statistical analyses with no disclosures of specific individuals.

18.2 Ancillary Studies

18.2.1 Definition of an Ancillary Study

An ancillary study is a research study which is characterized by one or more of the following: (1) observations or procedures supplementary to the DISC Protocol to be performed on all or a subgroup of participants in the trial according to a set protocol, or (2) additional work to be done by, or information to be obtained from, the Coordinating Center. Ancillary studies are encouraged since they enhance the value of DISC and encourage the continued interest of the investigators.

Either one, several, or all DISC Clinical Centers may participate in a particular study. The Coordinating Center retains the option of participating in a

particular ancillary study. The Coordinating Center will not be expected to provide data entry and editing services nor data analysis for ancillary studies unless it agrees to participate as a full scientific partner.

18.2.2 Request for Approval of an Ancillary Study

Individual investigators desiring to perform ancillary studies are encouraged to do so. An investigator who wishes to undertake an ancillary study must prepare a brief formal research proposal. This proposal should contain statements on objectives, background, methods of study (including feasibility) and the facilities available. If the Coordinating Center has agreed to participate, the proposal should be accompanied by a statement from the Coordinating Center indicating its commitment of services to the study.

Proposals for ancillary studies are to be submitted to the Design and Analysis Committee for preliminary review. Copies of the proposal should be made available to all members of the Design and Analysis Committee one week prior to the meeting at which it is to be considered. The primary objective is to review the compatibility of the ancillary study with the DISC Protocol.

Before an ancillary study can be approved, it must be shown that the ancillary study will not:

1. Interfere with one or more of the procedures of the DISC Protocol.
2. Complicate interpretation of DISC results.
3. Adversely affect patient cooperation in DISC.
4. Jeopardize the public image of DISC.
5. Create a serious diversion of study resources, either locally or centrally.

Questions on the proposal will be referred back to the applicant to allow the investigator to amplify, clarify, and/or withdraw the request. The Design and Analysis Committee will make a recommendation to the Steering Committee on the approval or disapproval of the proposed study. A proposal which has received

conditional approval must be resubmitted to the Design and Analysis Committee for final consideration. After the final review of the proposal, the Steering Committee will prepare a statement of its consensus, including any reservations or objections, and forward it to the investigator who requested approval for the ancillary study.

Those proposals which are judged compatible with the DISC Protocol are submitted to the Data and Safety Monitoring Committee for review of their scientific merit and also the compatibility of the proposed studies with the DISC Protocol. In making the final recommendations concerning a proposed ancillary study, the Data and Safety Monitoring Committee will consider the possibility that participants in DISC might comprise a captive group for a study having little scientific merit.

18.2.3 Funding of an Ancillary Study

If additional funds are not required, the investigator may proceed with the ancillary study as soon as it has been approved by the Steering Committee. If additional funds are needed, the investigator may submit a research grant application to the Division of Research Grants for review in the same manner as any other new grant application. It is understood that the investigator will not accept the grant, or activate the ancillary study, until Steering Committee approval has been received.

18.2.4 Ancillary Studies by Others

Each investigator will regard the use of the study participants for ancillary studies to be performed by local colleagues in the same light as the investigator's own research. This is, to the extent the investigator can control the use of participants for study purposes, others will not be permitted to carry out ancillary studies unless prior Steering Committee approval has been obtained.

18.2.5 Publication of Ancillary Studies

Since the criteria for approval of ancillary studies does not include scientific merit, all reports of ancillary studies to be published or presented must be approved by the same publication review and approval process as other DISC publications. This review will determine whether the publication or presentation of the ancillary study adversely reflects on the study as a whole. If it is determined that the publication adversely reflects on the study, all such reports must delete reference to the DISC cooperative group before publication.

18.3 Referral Policy

Referral policies for ineligibles are outlined in Section 4.5 along with the conditions meriting referral to an appropriate health professional. These policies will remain in effect for any of the listed conditions which may develop after a child has been enrolled in DISC. Clinical monitoring and referral policies for DISC II are detailed in Chapter 9.

18.4 Copyrights and the Use of Standardized Instruments

When instruments used in DISC are copyrighted, two different estimates of the costs involved in their use should be made. In most instances out-right purchase of necessary materials from vendors will not be prohibitively expensive, even for a large sample. Nevertheless, companies should be contacted and asked about fees charged for photocopying privileges, especially in the reproduction of answer sheets which cannot be reused. Attempts should be made to explain to them the

wide-scale exposure that the instrument will receive in DISC, and the fact that the study is government sponsored and non-profit.

In instances where an instrument has not been copyrighted and sold commercially, DISC should extend to authors the courtesy of contacting them and keeping them informed of the instrument's use. If minor modifications of the instruments have been made in order to adapt them to the DISC population, copies of the revised test should be sent to the original authors after pretesting is complete.

05/12/95

CHAPTER 19

PROCEDURES FOR DISC PARTICIPANTS
WHO ARE PREGNANT OR WHO HAVE RECENTLY GIVEN BIRTH

DISC will see a number of girls who are pregnant or who have given birth recently. Staff members should be sensitive to their concerns, make them comfortable, and assure them that their continued participation in DISC is valued.

19.1 Annual Data Collection Visits

The following procedures should be used for annual data collection visits.

19.1.1 If clinic staff learn that a girl is pregnant or lactating before the annual or final data collection visit is scheduled:

- a. Call to schedule the visit as soon as possible. Assure the participant that DISC is still interested in her. If a blood draw is scheduled, tell the participant that her blood will not be drawn, and that she should not fast before the visit. If possible, the visit can be re-scheduled (either within or outside of the visit window, when necessary) to measure the participant three months post-partum or post-lactation.
- b. Notify the DISC clinic interventionist as soon as possible that a participant is pregnant or lactating and give him/her the ID and namecode of the participant.
- c. Do not mail the menses calendars, if they are scheduled for the visit.
- d. At the data collection visit, measure the girl's height and record her pregnant condition in the Revised Stature and Maturity Form or the Final Visit 01 Physical Exam Form. Administer the Participant History and/or the Participant Medical Information Follow-up Form. Omit all other measures. Clinic physicians should not do a physical exam or perform any

other medical procedures on a girl who is pregnant. Complete a DISC II Annual Visit Summary or the Final Visit 01 Summary Form and record the reason for missing measures and forms as "pregnancy" or "lactation".

- e. Do not give the girl menses calendars for the post-visit six weeks.
- f. Get information on the girl's estimated delivery date, and her plans for the future to make locating and scheduling for the next annual visit easier. The next annual visit should be scheduled no earlier than three months post-partum or post-lactation.

19.1.2 If the clinic staff learn that a girl is currently pregnant or lactating at the clinic visit:

- a. Measure only the girl's height and record her pregnant condition on the Revised Stature and Maturity Form or the Final Visit 01 Physical Exam Form. Administer the Participant Medical History Follow-up Form and/or the Participant History. Omit all other measures. Clinic physicians should not do a physical exam or perform any other medical procedures on a girl who is pregnant. Complete a DISC Annual Visit Summary Form or a Final Visit 01 Summary Form, and record "pregnancy" or "lactation" as the reason for missing measures or forms.
- b. Review any menses calendars that might have been returned before the visit with the girl. Do not give the girl menses calendars for the post-visit six weeks.
- c. Get information on the girl's estimated delivery date, and her plans for the future to make locating and scheduling for the next annual visit easier. The next annual visit should be scheduled no earlier than three months post-partum or post-lactation.
- d. Notify the DISC interventionist as soon as possible that a participant is pregnant or lactating and give him/her the participant's ID and namecode.

19.2 INTERVENTION SESSIONS

The following procedures should be used for intervention sessions or activities:

- 1.The collection of NCC and NDS food recalls, the Case Management Form, the Diet Acceptability Forms, and the measurement of weight at intervention sessions should be omitted until three months post-partum or post-lactation. The Participant Tracking Form should be completed, and the measurement of height at intervention sessions should be carried out as usual.
- 2.If intervention staff learn independently that an intervention group participant is pregnant or lactating, they should notify an UNBLINDED member of the clinic data collection staff so that plans for the next data collection visit can be made in advance.