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CHAPTER 1

OVERVIEW OF STUDY AND DATA COLLECTION PRIORITIES

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 death 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 38 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 (DISC) 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 STUDY OBJECTIVES

The primary objectives of DISC are to assess feasibility, acceptability, efficacy, and safety of dietary intervention in children age 8-10 with elevated 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 trial.

1.3 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 - 11/92): full-scale trial

Phase III (12/92 - 11/93): 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. 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 a 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 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.

1.4 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 80^{th} to 98^{th} percentile range will be enrolled. Exclusion criteria include obesity (weight for height greater than 90^{th} 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.

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.

1.5 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. However, 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 12 initial group intervention sessions, families will be asked to attend monthly maintenance sessions. 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. In DISC II the same intervention goals will be used with the exception of the goal for dietary cholesterol where the 150 mg/day limit will be 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.

1.6 VISIT SCHEDULE AND TYPES OF INFORMATION COLLECTED

Eligibility of prospective participants will be determined during a series of three screening and baseline visits. Prior to the first is a prescreen for elevated plasma total cholesterol either using a desktop cholesterol analyzer on a capillary blood sample or analyzing a venous blood sample at a local laboratory. Venous blood samples will be taken at the first and second screening visits 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 the first and second screening visits. Eligible volunteers will be

asked to attend a baseline visit 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 for 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.

1.7 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, 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 University in Baltimore, Central Laboratories for nonlipid determinations at Johns Hopkins University 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 Planning/Steering Committee comprised of investigators from each Clinical Center, the Coordinating Center, and the Program Office, with oversight by a Data and Safety Monitoring Committee comprised of scientists not directly associated with DISC.

1.8 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, 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 assessment (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.

If the participant will not come in for a clinic visit, attempts should be made to obtain a home visit. There the non-clinic visit procedures and the priority ranking shown above for obtaining data should be used.

Clinic personnel should be creative in trying to get, at a minimum, the highest priority data on all DISC I participants for the 36-month

visit. This may mean obtaining data outside the 36-month visit window, having another person call, offering additional incentives, spending time discussing barriers to participation and how they can be resolved, assuring confidentiality, making a home visit, accommodating the family's schedule, or other means that can be thought of. Case conferences with each center, or discussions with DISC personnel at other centers, may be very helpful in dealing with difficult cases. It also may be helpful for the Principal Investigator to call the parent or child directly.

When enrolling the participant for DISC II, for difficult cases it can be agreed to let the participant continue yet not provide all the data, if he/she will not continue otherwise. For example, if a participant will continue for DISC II only if Tanner staging is not done, it is permissible to agree to that condition in order to get the participant to continue. Any of the measures can be bargained with in order to get the participant to continue. Secondary priority items should be bargained with first. If the participant or parent refuses to sign the informed consent form, the form can be modified to indicate for which measurements consent is not being given. Permission to obtain those measurements can be pursued again at subsequent visits at the discretion of DISC clinic staff, in which case if the consent form has been modified, a new consent form should be signed. For participants assigned to the intervention group who say they don't want to continue in the study because they don't want to come to the intervention sessions, it is permissible to say that attendance at intervention sessions is encouraged, but not required.

1.9 REFERENCES

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