CHAPTER 25

THE MULTICENTER APPROACH TO HUMAN FEEDING STUDIES

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Feeding studies form an essential link in the lines of evidence that establish causal relationships between diet and disease risk factors because the degree of dietary control is unparalleled by any other type of nutrition intervention. Along with other nutrition studies, feeding studies provide data that subsequently are used by health professionals to develop dietary recommendations for the public. At times, however, study findings are inconsistent because human feeding studies usually have small sample sizes and often use different experimental designs. The result is that the public may perceive a mixed message that can lead to confusion about optimal nutrition.

One strategy to minimize conflicting scientific reports is to conduct large, well-controlled feeding studies, using the model of the multicenter clinical trial in which several field centers follow a common dietary protocol. This approach allows for human feeding studies with adequate sample size and broad representation of the population.

This chapter describes several recently completed multicenter studies; provides information on the rationale, organization, and function of such studies; considers issues of quality control and cost; and discusses implementation of the dietary component of multicenter feeding studies.

EXAMPLES OF MULTICENTER FEEDING STUDIES

To date, few multicenter feeding studies have been conducted and they vary considerably in size and scope. Two large-scale studies were Dietary Effects on Lipoproteins and Thrombogenic Activity (DELTA) and Dietary Approaches to Stop Hypertension (DASH), both sponsored by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health. Throughout the chapter, examples from DELTA and DASH are used to illustrate the multicenter feeding study approach.

The DELTA program (1992-1996), a multicenter, collaborative human feeding study with rigorous standardization and monitoring of diet composition (1), was initiated to study the effects of dietary fat modifications on plasma lipids and lipoproteins and markers of thrombogenesis. The need for this study derived from uncertainties about the efficacy of reduced-saturated-fat diets for all segments of the population. There were numerous clinical investigations of the effectiveness of a reduced-saturated-fat diet in lowering blood cholesterol levels in men. However, far fewer studies had been conducted in women. In addition, little information was available for different age and ethnic groups, and for individuals with clinical disease or other elevated risk factors. This paucity of information highlighted the need for larger studies, which could be achieved by using a multicenter collaborative effort.

In DELTA, two protocols were developed to answer separate research questions for two distinctly defined populations. The first DELTA protocol examined the effects on blood lipids and hemostatic factors of three levels of total and saturated fat in 103 normolipidemic participants from several demographic subgroups, including pre- and post-menopausal women, men, Caucasians, and African-Americans (2). The

second protocol evaluated the response to diet of lipids and hemostatic factors in 86 adults with biomarkers of dyslipidemia/insulin resistance (low high-density lipoprotein cholesterol and elevated triglyceride and serum insulin levels). Three experimental diets were fed: an average American diet, a diet low in saturated fat and high in total fat and monounsaturated fatty acids, and another low-saturated fat diet that was also low in total fat and high in carbohydrate and fiber (3).

The DASH study (1993-1997) tested the effect of three dietary patterns on blood pressure in 459 adults using a randomized controlled human feeding trial design (4). The DASH study fed its participants an average American diet, a high-fruit-and-vegetable diet, and a low-fat, ''combination'' diet high in fruits, vegetables, and dairy products.

Based on many previous studies, the efficacy in lowering blood pressure of caloric restriction for weight reduction and of reduced consumption of alcohol and sodium is generally well accepted and forms the basis for nutritional recommendations for preventing and treating high blood pressure (5, 6). Epidemiologic studies on other diet-related factors and blood pressure have reported significant associations. These factors included micronutrients such as potassium, calcium, and magnesium (inversely related to blood pressure); macronutrients such as amount of dietary fat (directly related) and protein (inversely related); and dietary fiber (inversely related). However, the results from randomized controlled clinical trials testing these dietary factors singly have been inconsistent and equivocal. In contrast, the blood pressure-lowering effect of a vegetarian dietary pattern has been consistent. This evidence provided the basis for the DASH study to test the efficacy of dietary patterns in reducing blood pressure. To achieve a sample size sufficient to allow adequate representation of women and minorities, particularly African-Americans for whom high blood pressure is a major public health problem, a collaborative multicenter effort was required.

The multicenter approach was also used recently for a large industry-sponsored study examining the efficacy of commercially prepared complete diets for nutritional management of cardiovascular risk factors (7). Food prepared at a central location (Campbell Center for Nutrition and Wellness, Campbell Soup Company, Camden, NJ) was shipped to 10 clinical centers, where it was distributed to 283 adults with hypertension, dyslipidemia or diabetes. The participants in the active intervention group were instructed to supplement the centrally prepared breakfast, lunch, dinner, and snack menus with specific quantities of self-obtained fruit, vegetables, and dairy products. Values for risk factors (such as blood pressure, weight, plasma lipids, and plasma glucose) during baseline and treatment periods in these subjects were compared with values for 277 control subjects whose treatment was a completely self-selected version of a similar therapeutic diet.

Other multicenter human feeding studies that have been reported were smaller in scope. A NASA-sponsored study of zinc and copper balance during long-term bedrest enrolled a total of 7 participants at two centers because of limited bed availability and the high amount of care required for study participants. To ensure similar food preparation between the centers, both dietary staffs were trained to use the same techniques for weighing and preparing the foods (8). Food aliquots were analyzed before and throughout the 29-week study, confirming the good correlation in the mineral content of the experimental diets prepared between the metabolic kitchens.

Another example is a four-center randomized crossover feeding study that examined the effects of carbohydrate content on glycemia and plasma lipoproteins in 42 patients with non-insulin-dependent (type 2) diabetes mellitus (9). Standardized diets were prepared in four metabolic kitchens and plasma samples from each site were shipped to various laboratories for analyses of lipids, lipoproteins, and insulin levels.

Scientific Rationale for Multicenter Studies

The typical single-center human feeding study has a small sample size from a narrowly defined population. Because these studies are expensive and require a large investment of time, labor, and space, it generally is difficult for a single investigator funded by a research grant to enroll, feed, and study more than 20 to 25 participants at one time. This maximum imposes constraints on study duration and design. Consequently, many human feeding studies lack sufficient statistical power to detect small, but biologically meaningful, differences among groups or treatments. The relationship between sample size and the ability to detect small effects has been described in Chapter 2, ''Statistical Aspects of Controlled Diet Studies.''

One way of accruing sufficient sample size to estimate the quantitative effect of diet on physiological parameters is through meta-analysis techniques that combine data from different studies that sought to answer the same scientific question. However, often the various studies are not comparable. They employ different experimental designs and vary with respect to dietary modification, length of intervention, participant inclusion and exclusion criteria, and inclusion of control groups. These factors, among others, affect the findings and conclusions made in each study. A multicenter feeding study, by using a common protocol, is able to pool data collected at different centers and thus has a large sample size and high statistical power to detect a small effect size.

The DASH investigators wanted high statistical power (power = 85%) to detect a reduction of 2.0 mm Hg in diastolic blood pressure in response to the dietary treatments (4). To detect this difference a minimum of 405 participants, or 135 in each of three treatment groups, was required. During a 2-year period each field center was required to randomize a total of approximately 120 participants, allowing for dropouts. Five cohorts of 20 to 30 participants

were studied at each of the 4 field centers. This allowed feasible management of the participants by the staff.

Because they can accommodate a large sample size, multicenter studies can complete a protocol in a shorter time period overall than would be possible for a single study site. For example, a crossover design requiring 80 to 100 participants for adequate statistical power would take 4 years to complete if only 20 persons could be studied at a time, but only 1 year if 4 centers worked simultaneously. With a multicenter study design participants are enrolled concurrently among the centers, and the entire study can be completed in a shorter time period than in single-center studies.

The small sample size in single-center studies also places constraints on the population groups that can be included. To minimize sources of variability and factors that might affect the dietary response and reduce statistical power, investigators usually study a homogeneous population. For example, many previous diet studies were conducted with young Caucasian males. Much less is known, therefore, about how other population groups respond to dietary changes. Studies of dietary response as affected by sex, age, race, comorbid conditions (such as obesity), genetic profiles, and other factors ultimately provide evidence for dietary recommendations that are applicable to a broader population. The DELTA protocols found that plasma lipid responses to the experimental diets were similar for men and women of different ages and for Caucasians and African-Americans (2). Similarly, the results of DASH showed that the experimental diets lowered blood pressure in men and women, in minorities and nonminorities, and in individuals who had and did not have hypertension (10).

The Multicenter Model: Organization and Operation

The organization and operation of randomized controlled trials stems from their overall purpose, testing the effectiveness of an experimental drug, procedure, or other treatment (11), and when several clinical centers are needed to meet large sample size requirements, a multicenter study is instituted (12). These trials vary in size and extent, have a complex organizational structure, and are costly. However, they have the potential to yield data of high validity and detect small but important effects. Rigorous adherence to the protocol and manual of operations is central to performing the tasks in a standardized manner.

Multicenter feeding studies have a structure similar to that of multicenter clinical trials in that they include field centers in different geographical locations, centralized laboratories, a data coordinating center, and central coordination of activities (12). Figure 25–1 illustrates the organizational structures of the DELTA and DASH studies.

The operation of multicenter feeding studies also parallels that of multicenter clinical trials. In general, study investigators design one or more collaborative research protocols. *Field center* personnel prepare standardized experimental diets, feed participants, and use identical methods for data collection. *Central laboratories* may be used to ensure standardized analyses of food and biological samples and minimize interlaboratory variations. A *coordinating center* standardizes management and data collection procedures, oversees a centralized quality control program for all aspects of the study, and provides expertise in biostatistics to ensure sound approaches to study design and data analysis. For smaller multicenter studies, one field center also may act as the coordinating center. Table 25–1 summarizes the functions of the multicenter feeding study organizational units.

The primary governing body is the *steering committee*, which is composed of the principal investigator of each field center and the coordinating center and a sponsoring agency representative also known as the project officer or scientist. The steering committee members are responsible for developing the study protocol, making scientific and policy decisions, facilitating the conduct of the study, and interpreting and reporting the study results. Members of the steering committee define rules regarding access and analysis of data from collaborative studies. Subcommittees of the steering committee are formed to address such issues as protocol development or design and analysis, recruitment, measurement, quality control, diet design and management, and publications. Work is managed through numerous conference calls and periodic meetings. Additionally, an independent *data and safety monitoring board* usually is appointed by the sponsor to review progress, monitor safety, and assess the significance of preliminary results. Administrative and scientific oversight of the entire study are provided by the *sponsoring agency.*

The coordinating center staff make a major contribution to the statistical design of the study, the organization of study activities, and the preparation of the study protocol and the manual of operations. They have responsibility for developing and implementing standardized procedures to collect data from the field centers so that the data can be pooled for analysis. The coordinating center often arranges for centralized laboratory analyses of the biological specimens and experimental diet nutrient composition, and may play a role in developing plans for specimen and food composite transfer. The coordinating center oversees a study-wide quality control program, which ensures comparability and reliability of data and includes site visits, staff training and certification, and data monitoring. These quality assurances add to the higher costs for a multicenter project. Finally, the coordinating center personnel have the responsibility for analyzing data generated by the field centers and the centralized laboratories.

Field center interdisciplinary teams comprise senior investigators and coinvestigators; research dietitians; a study coordinator; recruiters; and kitchen, technical, and clerical staff. The main functions are to recruit and feed study participants and collect data. To do these tasks, they must have experience in recruiting and managing participants, preparing the diets, handling the food, evaluating compliance,

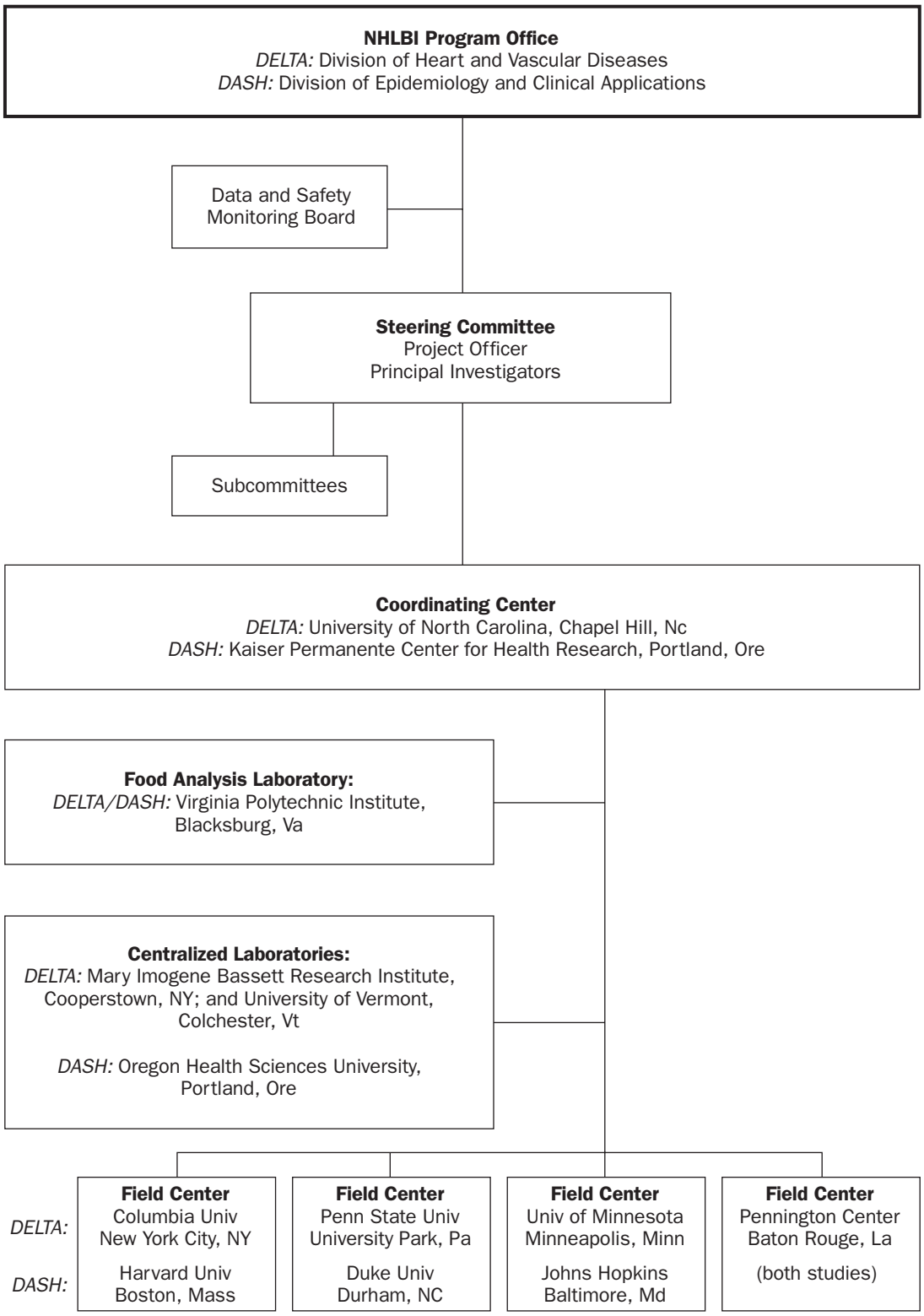

FIGURE 25-1. Organizational chart of multicenter feeding studies, DELTA and DASH, sponsored by the National Heart, Lung, and Blood Institute, Bethesda, Md.

TABLE 25-1

Functions of the Multicenter Feeding Study Organizational Units

Unit	Functions
Program office	Oversee administration and provide scientific oversight of project
Steering committee	Make policy decisions for the study Design study protocol, including dietary treatments and endpoint measurements Interpret data and report study results
Subcommittees	Develop procedures for implementing protocol Provide input to steering committee for design of study protocol, including dietary treatments, measurements, and data analyses
Coordinating center	Standardize data collection procedures Arrange for centralized laboratory analyses Prepare protocol and manual of operations Prepare and distribute forms Oversee quality control and staff training and certification Control data transfer and management Monitor and analyze data Arrange meetings and conference calls
Centralized laboratories	Analyze biological samples Conduct nutrient analyses of diets
Field centers	Adhere to all aspects of the protocol Recruit and enroll participants Prepare experimental diets Feed study participants Assess and ensure participant compliance Collect data Ship samples to centralized laboratories Transfer data to coordinating center
Data and safety monitoring board	Review study progress, monitor safety, and assess significance of preliminary results

collecting and handling biological specimens, and maintaining masked (blinded) designs.

Maintaining these designs is a critical element of all clinical trials. At the field centers, masking is preserved by keeping measurement staff unaware of the diet assignment and by keeping kitchen staff who know the diet assignment unaware of measurement results. Standardized laboratory analyses often are conducted at the field centers but may also be performed at a central laboratory. The field center personnel also are responsible for the shipment of food composites and biological samples to analytical laboratories outside the field center and for the expedient transfer of data to the coordinating center.

The Diet Subcommittee is composed of dietitians and nutritionists from the various study centers, as well as the individuals responsible for the food composition analyses. This subcommittee is instrumental in developing the dietary component of the protocol, including menus, standardized food preparation procedures, participant feeding procedures, and techniques for monitoring dietary compliance (Exhibit 25–1).

Costs and Quality Control in Multicenter Studies

The cost of conducting multicenter feeding studies is substantial. In addition to the high cost of laboratory analyses, there are expenses, similar to any feeding study, associated with labor, supplies, and time. Although there are some cost savings, expenditures are usually multiplied when several sites work together. Principal investigators, dietitians, study coordinators, and other professionals must meet to plan the study, develop a common protocol, and produce a manual of operations that specifies in detail how the study is to be implemented. Decisions must be made regarding which activities to centralize, how to standardize procedures, and how to monitor quality control. Unlike single-center studies, these decisions require considerable coordination, including frequent travel and conference calls. Study information and data must be mailed, faxed, or sent electronically to a coordinating center. The addition of a coordinating center, not

EXHIBIT 25-1

Issues Addressed by the Diet Subcommittee During the Planning Stage of the DASH Study

DIETARY TREATMENTS

Calculate costs of feeding
- 3 vs 4 diet treatments
- 8-week vs 12-week trial

Define ''usual'' or control nutrient levels
Recommend use of absolute nutrient levels or nutrient intakes indexed to energy needs
Establish nutrient targets
- fatty acids, cholesterol
- protein
- micronutrients
- fiber
- sodium

MENU DEVELOPMENT

Identify commonly used food sources for micronutrients
Consider soft drink micronutrient content
Determine how to control sodium intake
Discuss restrictions on water supply, if needed
Identify types of fruits/vegetables that will be acceptable to the study participants
Determine use of specific foods
- types of dairy products
- complex vs simple carbohydrates
- fortified foods
- margarine/*trans* fatty acids
- dietetic jelly and syrup

Set calorie levels
Develop unit foods as calorie adjustors
- define nutrient and calorie content

Select nutrient database
Develop recipes/menus according to guidelines
Taste-test recipes

MENU AND FOOD GUIDELINES

Define menu cycle
Specify portion control items
Select fresh, canned, or frozen fruits and vegetables
Establish consumption allowances
- alcohol
- caffeinated and other beverages
- spices and seasonings

Determine whether to adjust beverage consumption according to caloric needs

MENU VALIDATION STUDY

Determine nutrients to assay
Identify menus and calorie levels to prepare
Draft schedule
- cooking
- shipping
- chemical analysis

Specify diet preparation assignments
Obtain procedures, containers, and supplies from food analysis laboratory

(*continued*)

EXHIBIT 25-1

Continued

FEEDING LOGISTICS

Determine on-site and off-site meals
Discuss special meal situations
    weekend meals
    emergency meals
    holidays
Discuss procedures for packaging and serving foods
Discuss food safety precautions for staff and participants

FOOD PROCUREMENT AND PREPARATION

List foods with brand names/specifications
Specify centrally procured foods
Determine food industry participation
    identify and contact companies
    match company food items with menu items
    estimate amounts
Estimate food storage requirements
Decide on batch preparation techniques
Define cooking procedures
Calculate cooked weight portions
Establish guidelines for weighing foods

DIET ASSESSMENT PRIOR TO ENROLLMENT

Determine what type of information to gather
Select best method to gather information
Consider cost of administration, labor, materials, data evaluation
Decide when to collect information

SCREENING VISIT ACTIVITIES

Determine what information is required
    food allergies
    lactose intolerance
Determine how to assess whether the person will comply
    discuss menus
    assess food preferences, general dietary information
    assess usual eating habits (food frequency questionnaire; 3-day food record; other)
Decide when to administer forms and review data

CALORIC REQUIREMENTS OF PARTICIPANTS

Determine how to assess and calculate requirements
    equation to use
    physical activity assessment

WEIGHT MANAGEMENT DURING FEEDING

Define ''baseline weight''
Define ''stable weight''
Determine frequency of weight measurements
Decide when and how to adjust calories

(*continued*)

EXHIBIT 25-1

Continued

DIETARY COMPLIANCE

Describe compliance assessment
- foods not consumed
- nonstudy foods consumed
- missed meals
- sodium intake
- alcohol consumption
- attendance for on-site meals

Determine monitoring methods
- biochemical measures
- self-report

Define ''adequate compliance'' during run-in
Define noncompliance with intervention diet
Specify actions to take with noncompliance
Decide how to handle refusals to eat foods or meals
Prepare retrospective compliance questionnaire

MISCELLANEOUS ISSUES

Prepare study orientation meeting for participants
- when to conduct
- activities and issues to discuss
- prepare video about study and procedures

Establish exit interview and diet counseling at end of trial
Discuss incentives for participants
Discuss whether toothpaste with baking soda should be controlled
Determine interval needed between diet assignment and commencement of feeding
Design forms needed
Propose manuscripts

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necessary in a single-center study, also adds considerable costs to the overall study. Nevertheless, in return, data collected from multicenter feeding studies are of the highest quality because of the great deal of attention paid to quality control.

For any feeding study, chemical analyses of experimental diets strengthen the validity of the findings because the actual composition of the study diets may differ from the nutrient targets. Such discrepancies in nutrient composition (due to variations in food sources or errors in databases) may be sufficient to bias the results toward the null, ie, finding no effect, especially if the experimental diets have small contrasts (eg, 30% vs 26% kcal from total fat). For a multicenter study, however, validation and monitoring of the experimental diets are indispensable components of quality control, ensuring not only that the actual nutrient composition reflects the target goals but, perhaps even more importantly, that the study results can be pooled because the diets are the same at all centers.

OVERVIEW OF MULTICENTER TRIAL ACTIVITIES

The decision to launch a multicenter study is based on the significance of the problem, the need for a trial, and the feasibility of conducting the research (13). Once the study is initiated, it comprises a planning phase, an implementation phase, and a closeout phase.

During the planning phase the study protocol is designed through collaborative effort among scientists, clinicians, dietitians, and statisticians. If the study was initiated in response to a sponsor's solicitation, the protocol usually is derived from the research designs proposed in the successful grant applications or proposals but modified as necessary to develop a single common protocol. The investigators in multicenter feeding studies must agree to a common protocol in order to answer the research question(s).

Protocol development includes defining or refining the main hypotheses or research questions of the study. This will

guide decisions related to experimental design, sample size calculations, randomization procedures, dietary treatments, eligibility criteria, duration of intervention, endpoint measurements, and statistical analyses. Subsequently, recruitment strategies, data forms, manual of operations, and quality control procedures are developed. Exhibit 25–1 lists the diet-related issues and tasks discussed during the planning phase of DASH. The entire planning process is lengthy, detailed, and often tedious in that it requires careful consideration of many proposed approaches, but it ultimately yields a study design that is based on the strengths and experiences of all the people involved.

In finalizing the study design and protocol, a pilot study might be necessary. For example, in DELTA the question arose about whether diet composition could be standardized to a sufficiently precise degree among the four field centers. Consequently, a pilot study was carried out to evaluate two approaches to food procurement and preparation (14). The first approach employed central procurement of primary food sources of fat and cholesterol, with preparation of cooked entrees and baked goods at a single location. All other foods were procured and prepared locally according to standard specifications. The second approach had central procurement of the fat- and cholesterol-containing foods, local procurement of all other foods, and local preparation of all foods. Each field center prepared several menus using both approaches. The chemical analysis results showed that the second approach achieved nutrient targets and yielded sufficiently standardized diet composition among the field centers. The steering committee subsequently decided that the study kitchens should *locally prepare* all foods but *centrally procure* the key foods that might be major sources of variability in fat and cholesterol content.

Following the planning stage, the field center staff implements the protocol. Activities include recruitment, random assignment of study participants to the treatments, compliance monitoring, measuring implementation and outcomes, and monitoring quality control and results. Food preparation procedures and methods of determining participant compliance to the diets are observed closely by the kitchen and dietary staffs. Standardized data collection procedures, including the methods and frequency of acquisition and transfer of data, are followed. To ensure compliance with the protocol all procedures and data collection forms are monitored during regular site visits by the coordinating center.

After all participants complete the study, a number of activities occur during the final phase or ''close-out'' period. Field center investigators review and interpret their data in collaboration with the coordinating center staff who continue data management activities, verify the accuracy of the data, and conduct the statistical analysis. The coordinating center personnel also support manuscript preparation efforts through data analysis, statistical consultation, editorial activities, and coordination of meetings. At the conclusion of the trial, field centers usually inform the participants of the study results.

Implementing the Multicenter Dietary Intervention

The steps described here for planning and implementing the dietary components of multicenter feeding trials are similar to those for all well-controlled feeding studies. However, several unique issues must be considered with respect to staffing, facilities, equipment, menu development, food procurement and storage, food preparation, and participant management. Field center dissimilarities offer challenges both in implementing a common protocol and in standardizing methods of food preparation and delivery.

Facilities and Staff

Most likely, field center kitchens will differ in staffing patterns, size, production capacity, and equipment. Facilities can range from a metabolic kitchen at a clinical research center to a university food preparation teaching laboratory. At some research institutions the kitchens are designed specifically for conducting large-scale feeding studies. Field centers without an on-site kitchen may contract with a nearby hospital or another facility for use of the institutional kitchen. For DASH, Johns Hopkins University in Baltimore, Md, contracted with the Human Studies Facility at the US Department of Agriculture Human Nutrition Research Center, Beltsville, Md, to prepare the foods. Those foods then were transported to the feeding facility in Baltimore.

Every research kitchen has its own unique system of staffing. Facilities with a small number of foodservice employees may hire temporary or student help as needed for each project, but at some locations labor union rules may prohibit this practice. Sites with multiple funding sources may use their foodservice staff for consecutive projects. As for all grant-supported projects, it is imperative that the staff realize that their positions and length of employment are dependent on the funding period. Careful planning determines the number of staff required and their period of employment.

For example, if a site is required to feed 60 participants per year for 12-week periods, either two cohorts of 30 people or three cohorts of 20 people may be completed. The total number of weeks for study activity will be minimized by feeding two cohorts per year. Between cohorts the kitchen staff will become unemployed or available for another study. Alternatively, three smaller cohorts will use fewer staff more consistently, and the weeks between cohorts can be used for vacations, holidays, or other short assignments. Although some multicenter feeding studies will allow flexibility when the cohorts are completed, others may dictate the start and end dates for every cohort.

Food preparation procedures must be evaluated with respect to available facilities and staff at each field center. Menus that include many baked items might be problematic for field centers with limited access to ovens. For research kitchens with limited staff, it might be difficult to prepare

complicated recipes. Similarly, precision weighing of many food items translates into higher labor costs and may place another burden on some field centers. The use of items that are packaged in discrete portion sizes for noncritical foods alleviates the burden. Batch preparation of homogeneous foods or the use of pre-prepared foods such as muffins also may minimize labor efforts.

Menu Development

Perhaps the most challenging aspect of multicenter feeding studies is menu development. The menus and methods of food preparation must permit implementation of a common protocol in different settings. Field center dietitians must select the optimal approach for preparing and delivering research diets to the participants in terms of nutrient control, acceptability, and feasibility. For example, the meals must be easy to prepare within the constraints of the budget and of the research kitchen staff and facilities. The approach that meets these criteria, and also provides acceptable foods and minimal nutrient variability, is the best choice for multicenter feeding trials.

As with all feeding studies, the foods presented to the research volunteers must be acceptable or dietary compliance will suffer. In multicenter studies, regional and cultural food preferences may have considerable impact on menu development. To address this issue in DELTA and DASH, each field center dietitian developed several menus for possible use in the weekly cycle. The menus were then entered into one nutrient database program and were adjusted to meet target nutrients. After all diet subcommittee members reviewed the menus, modifications were made as needed. Selected food items were taste-tested at all field centers, and those foods found unacceptable were modified or replaced.

For example, in DELTA, the Louisiana participants preferred spicier foods than participants in the other field centers. Therefore, individuals were allowed to add seasonings (eg, hot pepper sauce). The Louisiana dietitians also originally developed a menu in which cornbread was served with chili, but taste testers at one northern center found that combination odd. As a result, cornbread was removed from the menu because it was not acceptable to all prospective participants.

The availability of foods at each field center also affects menu planning for a multicenter feeding trial. To provide diets that are as consistent as possible in nutrient composition, brand names are specified. However, not all brand name foods are available in each region of the country. Alternate brands that are similar in nutrient composition must be identified. The use of fresh, frozen, or canned foods also must be compared for possible nutrient variability, cost, preparation, and acceptability. For example, some kitchen managers prefer to use fresh mushrooms; others prefer the cost and time savings of canned mushrooms. For a study such as DELTA in which fats were the nutrients of interest, the type of mushroom used did not matter. However, if sodium were to be controlled, the food product specifications would have to indicate the form of mushrooms (canned, dried, fresh).

Finally, the inherent variability of food components provides challenges for maintaining identical experimental diets. Various combinations of central or local procurement and preparation provide several options for controlling the diet. Centralized procurement and preparation of foods offer the greatest control of nutrient variability but could result in higher cost, increased efforts in distribution coordination, and foods of lower acceptability. Foods highly variable in a critical nutrient are the most likely to require central procurement with distribution to the feeding sites.

The experimental treatments for DELTA required manipulations in the fatty acid composition of the diets. To minimize the considerable variability of this nutrient, all major sources of fat in the experimental diets were procured centrally (1, 15, 16). Those foods included meat, fish, poultry, margarine, butter, oils, dairy products except fluid milk, bread, and other grain products. Each field center was required to identify a local dairy that provided both skim and whole milk within the study specifications. All other foods were procured locally or were obtained through donations. (Also see Overview of Multicenter Study Activities.)

Chemical Verification of Diets

The food composition laboratory in a multicenter feeding trial establishes the effective premise of the study, that the nutrient content of the experimental diets will be sufficiently comparable across the feeding centers to be considered identical (1). This assurance is developed in two stages. First, during menu development the nutrient content of the diets is estimated with food composition databases and chemically analyzed to verify that the actual chemical composition meets the target values established by the study design.

Second, throughout the study the food analysis laboratory conducts ongoing quality assurance monitoring of each field center by assessing critical nutrients in randomly assigned composites of the experimental diets. Sources of variance in diet composition include daily differences among menus, market turnover, seasonal food supplies, commercial food product packaging, preparation techniques, assay procedures, and variation among calorie levels. The potential for variation among the field centers is unique to multicenter feeding studies. Each center may experience each source of variation but not necessarily to the same extent. This complicates the process of preparing identical diets but does not necessarily hinder the provision of experimental diets that meet nutrient specifications (1, 14).

Food Procurement

Procurement of food for multicenter studies requires careful planning and implementation because all sites must use the same food items. Food specifications must be reviewed by all to ensure that there are no regional differences in inter-

pretation that might affect nutrient composition. For example, two of the four DELTA centers purchased parboiled rice when ''rice, white, uncooked'' was specified because in their geographical regions, parboiled rice is most commonly used. The other two centers purchased white uncooked (not parboiled) rice. As noted previously, during menu development all sites should be familiar with their possible food procurement options to avoid using food items that cannot be procured by all field centers. Food source options include national institutional or retail distributors, individual retail grocers, or food companies.

Although food donations might appear to be a way of saving funds, the time necessary to make contacts and to orchestrate deliveries to each field center location is extensive. Based on our experience with DELTA and DASH, coordination can take easily 6 to 9 months of planning and follow-up and may require a half-time person depending on the number of contacts and companies being solicited and the number of field centers involved. The principal investigators must commit this time in advance. There may be additional costs to the field centers associated with shipping the foods and with renting storage space. These expenses must be considered in deciding whether to solicit food donations. It may be less expensive to purchase some foods directly than to incure the hidden costs of donated items.

Unique problems with food procurement arise during a multicenter feeding study. For example, food usage may vary across centers. Several donated foods for the DELTA study were shipped to one field center, and the staff at that site packaged and sent the foods to the other field centers. One field center used more of the centrally procured foods than anticipated. Therefore, the other sites had to ship specified quantities of their supplies to that field center to make up the shortfall. When feeding studies span several years, food product composition must be monitored for consistency. Frequently, manufacturers redesign their food products and the nutrient composition may be modified. The feeding periods for DASH spanned two years, and during that time, a commercial zucchini lasagna used in a menu was discontinued by the company. An alternate product that closely matched the nutrient composition of the lasagna had to be identified for the remaining cohorts.

Food Storage

Every field center has differing sizes of storage areas available. For a multicenter feeding study, ample storage space must be available on site, but off-site storage can be used creatively. Adequate storage space is required when a particular food item, such as meat, is purchased for an entire feeding period before the study begins. In addition, storage space becomes a significant issue when foods are donated in large quantities because food companies prefer to minimize shipments to save money on transportation costs.

Dry goods storage space may be available at the research facility or obtained through negotiations elsewhere at the institution. Off-site storage is an option but must be suitable for food in terms of temperature and rodent control. The amount of refrigerated space also may be satisfactory in the research kitchen or readily available within the institution. Frequent deliveries of food, when possible, will decrease the amount of storage space required.

Sufficient freezer space was a major problem for all field centers participating in both DELTA and DASH. All meats for each DELTA feeding protocol were distributed once to each field center. At each DASH field center, twice yearly food donations of frozen fruits and vegetables required significant frozen storage space. Options for acquiring freezer space included negotiating the use of freezer space from within the institution, renting freezer space from a frozen food warehouse, leasing a generator refrigerator/freezer unit and maintaining it on site, or soliciting donated freezer space. With an off-site location, an employee with a vehicle must transfer the food items. In the DELTA study, off-site food storage locations posed a significant problem for the field center located in New York City and for the other northern field centers during heavy snow storms. Some frozen food warehouses will charge a fee for retrieving the food in addition to the monthly rental fee.

Food Preparation

In a multicenter feeding study, not only must menus and foods be similar at each field center, but also all foods must be prepared identically and cooking procedures must be standardized across the field centers.

Detailed food preparation procedures are essential. For example, draining times for canned fruits and cooling times for cooked vegetables must be defined. Conversely, it may be specified to weigh fruit with the liquid using a nonslotted spoon and to weigh vegetables in the frozen state. In the DASH trial, which controlled dietary potassium levels, it was important to specify whether potatoes were to be boiled with the skin on and then peeled, or boiled without the skin. The potassium content of the potatoes differed according to the technique used.

Food preparation techniques will vary with the type of equipment available in the research kitchens. Rice, for example, may be prepared on a cooktop or in a plug-in steamer. The yield of cooked rice from raw rice must be similar regardless of cooking method to ensure equality in the portions served among the field centers. Similarly, cooking procedures for other foods such as vegetables must be equivalent. The finished cooked product at each field center must be similar regardless of the method used.

Meal Delivery and Compliance Assessment

All study participants at the field centers must follow similar guidelines for allowed ''free foods,'' beverages, and seasonings. Limits for alcohol and caffeine consumption must be

identical among field centers. Guidelines also are needed for discretionary or mandatory use of unit foods, which are specially prepared foods that have the same nutrient composition as that of the diet and provide needed calories. Dietitians in multicenter feeding studies may follow established methods to adjust participants' calorie levels for weight maintenance. The number of on-site meals may be specified, as well as which meal(s) must be consumed on-site.

Departures from the feeding protocol should be handled similarly among the field centers. For example, dietary compliance before randomization was assessed in DASH during a 3-week run-in period. The number of missed meals and foods allowed before removing a participant from the trial prior to randomization was defined (17). During intervention, specific guidelines for foods not consumed and nonstudy foods consumed were used to assess compliance to the diet.

To assist with compliance assessment, methods for recording dietary intake and adherence information are established by the diet subcommittee, and the forms needed are provided by the coordinating center. Daily food diaries that are completed by the study participants may be designed to identify deviations from the experimental diet, and other information such as number of unit foods eaten, the amount of alcohol consumed, or the number of salt packets used. Forms to monitor weight and calories consumed also are helpful in providing clues about dietary adherence.

Planning Time Line

A time line facilitates the coordination of planning activities. Much of the impending work depends on the completion of other activities. For example, menus cannot be designed until the nutrients of interest are defined. In turn, the nutrient composition of the experimental diets is guided by the study hypothesis. Figure 25–2 illustrates the time line used for planning the dietary component of the DASH study.

It is essential that the study hypothesis and the dietary treatments be defined as early as possible. Menu develop-

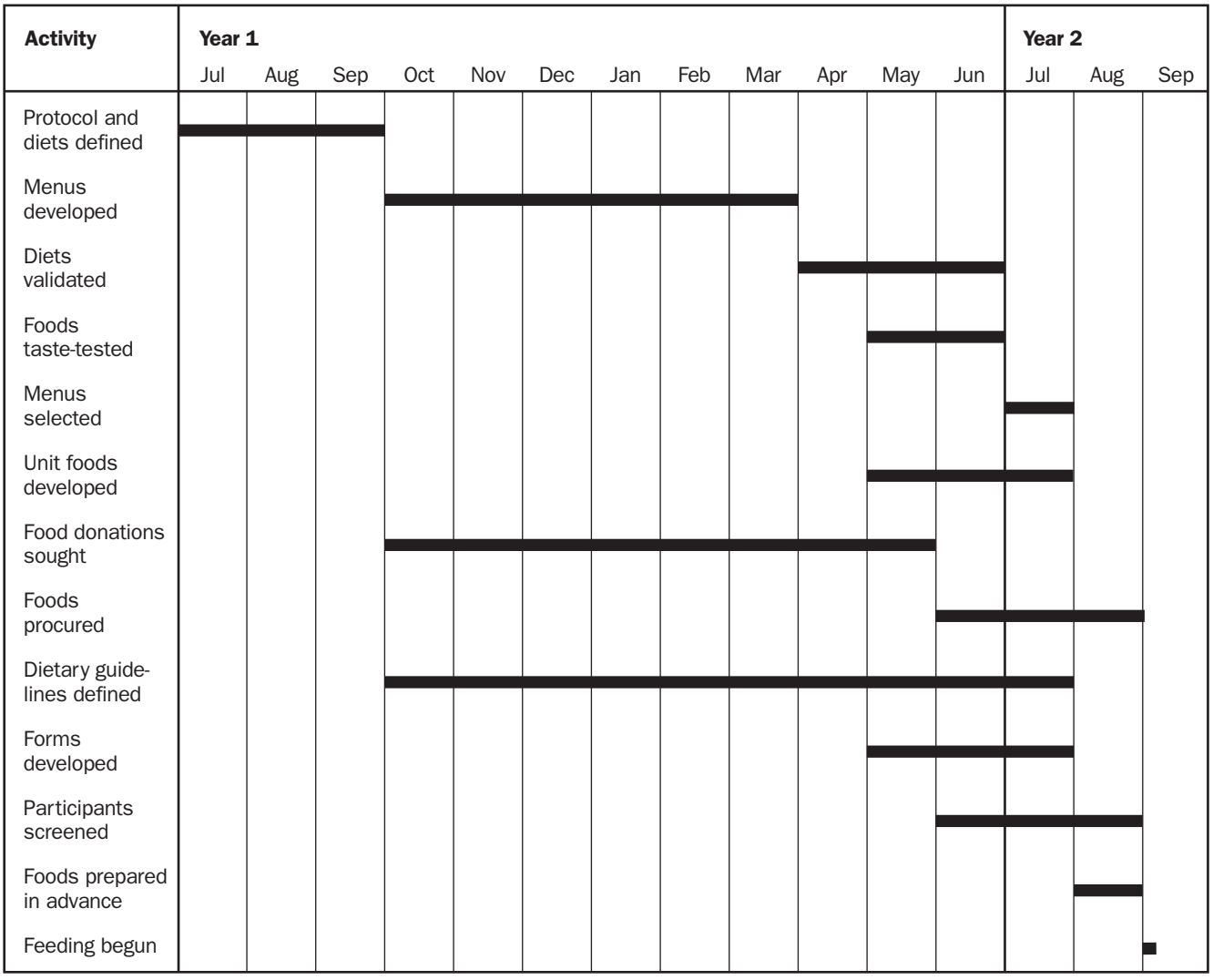

FIGURE 25-2. Planning time line for the dietary component of the DASH study.

TABLE 25-2

Diet-Related Forms Used for the DASH Study[1]

Form	Purpose
Study Food Checklist	Screening
General Dietary Information Questionnaire	Screening
Food Frequency Questionnaire	Screening/data collection
Study Menus	Screening/participant study information
Food Donation Tracking Form	Foodservice/procedural
Food Donation Contact Form	Foodservice/information
Food Inventory Control Form	Foodservice/procedural
Foodservice Sanitation Self-Inspection Checklist	Foodservice/quality assurance
Food Production Form	Foodservice/procedural/quality assurance
Tray Assembly Form	Foodservice/procedural/quality assurance
Orientation Form	Participant study information
Guidelines for Beverages and Seasonings	Participant study information
Safe Foods to Go	Participant study information
Daily Diary	Data collection
Compliance Assessment Form	Data collection
Body Weight and Energy Adjustment Form	Data collection
Post-study Anonymous Survey	Data collection

[1]Dietary Approaches to Stop Hypertension. *Forms Study Manual for DASH.* Portland, Ore: Dash Coordinating Center, Kaiser Permanente, Center for Health Research; 1995.

ment can take 6 months or more, depending on the complexity of the nutrient modifications. Time is needed to standardize food preparation techniques and recipes. Menus then are prepared for chemical validation, which may take 3 to 4 months to complete. Taste-testing may be conducted while the diets are analyzed, but menu modifications must not alter the nutrient composition. Otherwise, the chemical validation of the menu must be repeated. Based on the taste-testing and nutrient composition results, menus may be selected, deleted, or modified.

If food donations are pursued, possible contributors can be identified during menu development. Initial contacts can be made, but companies usually will not commit to donating foods until they know exact amounts that will be needed. Depending on the structure of the company, food donations may be approved and shipped quickly (within 2 months), but this process can take as long as 6 months.

Regardless of the procurement method, adequate time is needed to obtain foods before feeding begins. Arrangements must be made for purchasing foods from distributors or grocers. Depending on the facility, it could take several months to approve a billing system. For some institutions, such as the Pennington Center, foods must be placed on bid through the state purchasing office. The entire process takes approximately 3 months. It may be necessary to place food items on the bid, then remove them before the bid is awarded if the foods were on a deleted menu. Other foods needed because of menu changes but not on the original bid must be purchased separately or placed on a subsequent bid.

While menus are developed and validated, standardized guidelines may be established for allowed intakes of free and restricted foods and beverages, and procedures are developed for diet delivery and compliance assessment. Forms needed for the study are also designed and completed at this time. A list of diet-related forms used for the DASH study is given in Table 25–2. Field center dietitians most likely will be involved in participant recruitment and screening procedures. Then, a month before feeding, kitchen staff members are trained and may begin to prepare some foods that can be stored until needed. Finally, the day arrives when participant feeding begins. The unexpected may occur, but a multicenter feeding study that is carefully planned can be executed efficiently and effectively.

CONCLUSION

Similar to well-controlled single-center feeding studies, multicenter feeding studies seek to answer research questions about how diet affects metabolic parameters and disease risk factors. Their unique feature is that they are modeled after standard multicenter clinical trials. They have multiple feeding sites, usually located in different geographic areas, and thus can have a large sample size drawn from a diverse population, resulting in increased statistical power and enhanced generalizability. With this advantage, small, but biologically meaningful, differences among treatments have a higher likelihood of being detected.

Following the model of multicenter clinical trials, multicenter feeding studies have centralized laboratories and a coordinating center. Steering committees, composed of principal investigators and other professionals, design a common protocol and define the treatments and outcomes. The protocol is followed closely and the dietary treatments and pro-

cedures are the same for all centers. At the field centers, study participants are recruited and fed, and biological samples are collected and shipped to the centralized laboratories for analysis. The coordinating center provides administrative support, maintains quality control throughout the trial, and is responsible for the statistical analysis of the data. Quality control is a major component of study implementation and includes pre-feeding verification of the nutrient composition of study diets, during-feeding monitoring of the diets as fed at all field centers, and standardization of all data collection procedures. Although complex in design, costly, and time-demanding, multicenter feeding studies are good models for examining important and timely nutritional issues and controversies. The information gained from these studies can provide critical evidence necessary for developing dietary recommendations.

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