PART 3

# The Dietary Intervention

CHAPTER 10

# PLANNING DIET STUDIES

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Many types of diets and food preparation techniques are used in clinical and metabolic investigations. Some diets must be strictly controlled in order to detect small changes in outcome variables. Other diets may provide more flexible eating patterns and acceptable food choices for participants. Each has its place in nutrition research, but each has advantages and disadvantages that must be recognized and evaluated. This chapter describes the various types of research diets and their associated terminology, as well as the many factors that must be considered when study designers plan controlled diet studies.

## TYPES OF RESEARCH DIETS

Several classification systems can help to distinguish the types of research diets and dietary techniques that are used for human feeding studies.

### General Classification of Research Diets

#### *Formula Diets*

*Formula diets* are composed of basic foods or food components from a limited number of sources. A formula diet, repeated daily without variation for the duration of the study, offers the most rigid control and can be designed to accommodate the study of various nutrients (1). Liquid formula diets have been particularly useful for metabolic balance studies in clinical research. Chapter 14, ''Planning and Producing Formula Diets,'' contains a comprehensive description of formula diets and their application in human feeding studies.

#### *Conventional Food Diets*

In contrast to liquid formula diets, mixed diets composed of conventional food products permit a normal fashion of eating and thus are generally more acceptable to study participants. Conventional diets can be served according to several meal plans, as described here.

A *24-hour menu* consists of 3 to 6 meals repeated daily without variation for the duration of the study. Preparing and serving the same diet day after day minimizes fluctuation in nutrient composition, reduces the chance of error, and results in less confusion on the part of laboratory and kitchen staff. Metabolic balance studies usually require this type of diet plan to minimize variability (2). Also, frozen metabolic or constant diets that are provided to outpatients usually use this diet plan. However, the 24-hour menu plan may not be suitable for long-term studies because of its repetitive nature.

A *rotation* or *cycle menu* provides a specified number of daily menus that are repeated in an established sequence for the duration of the study. All of the menus have a similar nutrient content. Different menus have different foods, but each menu (and each food item within the menu) remains the same throughout the study. Menus typically are numbered to indicate the order of rotation through the cycle. To avoid confusion and minimize the chance of error, all participants are fed the same menu (eg, Menu Four) on the same day, regardless of their dietary treatment or when they enter the study. Problems would arise, for example, if there were ''rolling entry'' into a study (ie, subjects starting the protocol on different dates), and each participant began the study with Menu One.

*Ad libitum diets,* also called *self-selected, free,* or *habitual diets,* can be used for certain research purposes. The food items and amounts eaten are documented in a food record or food diary. This diet offers subjects the most variety, but it requires more computation time than other meal plans in order to analyze the participants' food records. In some cases participants are asked to weigh each food item to be consumed and to record the data, or the staff can weigh the foods in the kitchen and enter the data immediately into a computer. Duplicate portions of each food item may be collected and a composite of these foods analyzed for nutrients of interest.

### *Diets Used in Association with Clinical or Diagnostic Tests*

*Test diets* are meals of exact composition that are used to prepare the participant for specific types of diagnostic or research-oriented tests. These meals may be provided in an inpatient or an outpatient setting. One to 3 days' worth of meals may be given to a participant to eat at home prior to coming to the research center for testing. For example, meals of specific carbohydrate content may be served 1 day prior to an oral glucose tolerance test. Other examples of test diets include vanillylmandelic acid excretion tests; 5-hydroxyindoleacetic acid (5-HIAA) and serotonin restricted diets, fat malabsorption test diets; and high-calcium diets to define calcium intake in screening for hypercalciuria (3). Another test diet, one that has a specific aluminum content and is devoid of citrus, is consumed for 24 hours before deferoxamine infusion, a procedure for indirect measurement of aluminum stores (4). For some tests, a single meal of specific composition is required on the day of the test. For example, one meal of known magnesium content may be necessary for a 1-day study that requires intravenous administration of magnesium followed by collection of blood and urine.

Nutrient levels in test diets are not generally excessive in any given meal. Conversely, *load test meals* contain a specific nutrient(s) that may be excessive in relation to the amount typically consumed at any single meal. However, the load test meal does not have a nutrient amount that would be considered excessive for an entire day's intake. One example is the Fat Tolerance Test Meal, which contains a designated amount of fat (eg, 50 g) and typically a specific fatty acid composition (eg, an enhanced proportion of behenic acid). This load test meal is given at a designated time and blood is collected prior to and following the test meal to determine clearance of plasma chylomicrons. Other examples are the Oxalate Load Test Meal to test oxalate bioavailability in foods (5) and the Calcium Load Test Meal to test calcium absorption in hypercalciuria (6).

## The Diet Classification System of St Jeor and Bryan

The degree of control required for a diet study depends on study design, the type of study and its length, the emotional and physiological tolerance of the participants, laboratory and kitchen facilities, and the philosophy of the investigator. As St Jeor and Bryan (7) note, ''The investigator and research dietitian should be in agreement about the most efficient and successful way to achieve desired study results.''

All too frequently there is confusion regarding the terms used to describe research diets. One of the most problematic, for example, is the tendency to refer to all diets as ''metabolic diets.'' In an attempt to standardize the use of terms and define appropriate controls, St Jeor and Bryan (7) listed five basic types of diets—estimated, weighed, controlled-nutrient, constant, and metabolic balance—used in clinical research studies. These diets were named, described, and classified based on various dietary techniques used for calculation, measurement of diet, food source, water source, preparation procedures, food refusals, and need for laboratory analysis.

### *Estimated Diets*

The *estimated diet* relies on a visual estimation of a subject's food and fluid intake, which is then calculated for individual nutrients. This diet is the easiest to administer because it is closest to the self-selected or free diet. However, it is the least reliable because it estimates the participant's intake from equivalency lists or approximate nutrient values for foods measured in usual household (or hospital) portions. These diets may be planned by the research dietitian but are typically provided from a foodservice system other than the research center's facility (eg, the hospital food service).

### *Weighed Diets*

The *weighed diet* may also be served by the hospital food service; but food portions are weighed as served to the participant, and refuse is reweighed on return to the research kitchen. The difference in intake is then charted and nutrient intake calculated. This type of diet may be useful for macronutrient studies testing effects of protein, fat, or carbohydrate intake.

### *Controlled-Nutrient Diets*

The *controlled-nutrient diet* requires study nutrients to be maintained at a constant level throughout the study. Cooked

food items are weighed prior to consumption. If foods are refused, they are weighed when returned, nutrient composition of returned food is calculated, and nutrients are replaced.

Controlled-nutrient diets are more demanding of the dietitian's time because nutrients must be maintained at the same level throughout the study. Accurate calculations of daily menus are required, and food preparation procedures are controlled (but not as strictly as for the constant and metabolic diets). This type of diet may be used for long-term studies requiring a specific diet pattern but not rigidly controlled nutrient intake.

### *Constant Diets and Metabolic Balance Diets*

*Constant diets* and *metabolic balance diets* are the most rigorous forms of the controlled-nutrient diet. Procedures for diet calculation, food and beverage procurement, food preparation, patient instruction, and verification of nutrient content can be essentially identical for these two types of diets; they are equally demanding of the research kitchen. The distinct terminology indicates the type of research design for which the diets are used. *Metabolic balance diets* are used specifically for one type of research: nutrient balance studies (described later). In contrast, a wide variety of research designs, as well as diagnostic tests, may require a *constant diet,* which achieves constant (ie, minimally variable) nutrient intake through particularly close attention to food sources and preparation techniques.

The metabolic balance diet usually requires that nutrient data correspond with specific time periods (or phases) designated for collecting biological materials. The metabolic balance defines net gain or deficit of a particular nutrient or nutrients. The balance is said to be positive when dietary content exceeds loss in urine and feces and negative if losses in urine and feces exceed dietary intake. For a more detailed discussion, see Chapter 16, ''Compartmental Modeling, Stable Isotopes, and Balance Studies.''

The fundamental principle involved in the metabolic balance study is that of the ''single variable.'' By controlling all dietary intake and keeping the diet as constant as possible from day to day, any changes in balance may be attributed to the disease, procedure, medication, or nutrient under study. The nutrient content of a metabolic balance diet is assessed from a food composite made by preparing a duplicate portion of the subject's food and beverages for a single day. The reliability of metabolic balance data depends on caloric constancy and weight maintenance, a diet that achieves the desired nutrient composition, a fixed volume of food and fluid intake, stabilization on the diet, accurate urine and fecal collections, and control of physical activity and other stresses. Because of its rigorous demands, metabolic balance studies are best done in the setting of a research center equipped with a research kitchen and an analytical laboratory (8). The study design determines the acceptable level of variability in the research diet and, accordingly, the necessary degree of control and ''constancy.'' For example, some hypotheses can be tested only when the day-to-day coefficient of variation in nutrient content is very small; other hypotheses can tolerate more oscillation. Therefore, when the study is being planned, the levels of control provided by the different types of research diets should be evaluated and matched to the requirements of the protocol. Investigators may find that the most rigorous levels of control are needed for only short periods of time, and that a constant diet can be first preceded and then followed by a less burdensome, less expensive estimated or weighed diet.

The degree of dietary control depends on specific requirements of the study. Investigators adapt these classifications to accommodate the setting and the nutrient control necessary for the study, frequently combining or overlapping the methods to control intake.

## Phase Components of Diet Studies

Results from an experimental diet are often compared to those measured during *a baseline period.* This is typically a period just prior to the dietary treatment during which participants consume their usual (ie, self-selected) diets. Diet records are often taken during the baseline period so that outcome variables measured in association with the baseline period can be related to the habitual diet of the study population. This use of the term *baseline period* should not be confused with the baseline period required by some drug trials, in which the diet is kept constant throughout each of three phases: the ''baseline period'' (no drug), the ''trial period'' (drug treatment), and the ''off period'' (no drug).

A *run-in diet* or *stabilization diet* is an initial diet phase that provides a standardized intake for all participants. With this design, all participants begin intervention from the same diet; and the effects of any one eating style are minimized prior to feeding the experimental diets. The run-in diet is often patterned after current dietary patterns (eg, a typical American diet) or a reference diet (eg, the Step 1 diet of the National Cholesterol Education Program). This period adds another diet dimension for statistical comparison with subsequent feeding periods. (See Chapter 2, ''Statistical Aspects of Controlled Diet Studies,'' and see Chapter 6, ''Recruitment and Screening of Study Participants,'' for a discussion of use of the run-in diet during screening.)

When a response that is measured during one diet period is influenced by the previous diet, there has been a *carryover effect* or *diet order effect.* Preventing carryover effects is commonly accomplished by incorporating *washout periods* between experimental diet periods. Washout periods are nontreatment diet periods used to eliminate or minimize the nutrient carryover effect. Washout diets may be controlled diets that are patterned after the typical American diet, or they may be the participants' self-selected diets. Although washout periods between study diets can be used to reduce carryover effects, they may not be required when diets are randomly assigned and dietary treatments are of sufficient duration. In other words, the diet period must be long enough

for changes that had been induced by the previous diet to cease (Table 10-1) and for changes associated with the new diet to take effect. (See Chapter 2, ''Statistical Aspects of Controlled Diet Studies.'')

*Depletion diets* and *repletion diets* may be used to determine nutrient requirements or to determine the optimal effective dosage of specific medications. For example, a diet low in magnesium, sodium, and potassium may be required to deplete blood levels of these nutrients in preparation for comparing the effectiveness of three preparations of potassium-magnesium citrate in correcting hydrochlorothiazide induced hypokalemia and hypomagnesemia.

## Planning Considerations

Whether evaluating the feasibility of an existing protocol or planning a diet study from conception, the research dietitian and the principal investigator should give careful consideration to physical, financial, and human resources as they relate to the number, length, and order of dietary treatments; the range of calorie levels; and the recruitment of participants as inpatients or outpatients. Among the research team members, the dietitian is the best judge of how intricate the feeding phase can be without creating error-prone situations in production and delivery of meals.

## Inpatient and Outpatient Settings

Research that has a feeding component can be undertaken in different settings. Residential feeding studies where continuous supervision is possible are most often conducted in hospitals, but boarding schools, convents, and monasteries have also been used. Prisons, although theoretically well-situated for feeding studies, are usually not suitable; compliance is likely to be poor, and the element of coercion cannot be ruled out. (In some states, there is legislation that specifically prevents the enrollment of prisoners in research protocols.)

The advantages and disadvantages of all types of study settings must be carefully considered during protocol development. Balance studies or studies requiring frequent measurements are best conducted on an inpatient basis because it is easy to control exercise, supervise food and fluid intake, collect urine and stool specimens, and carry out timed blood collections. During inpatient studies, subjects have fewer temptations to eat unauthorized foods, often share a spirit of camaraderie with other subjects, and find it advantageous to have everything prepared for them. Investigators can easily verify compliance.

Outpatient studies, on the other hand, are much less expensive to conduct and much less disruptive to the subjects.

**TABLE 10-1**

**Length of Feeding Periods or Washout Periods for Selected Nutrients**

| Nutrient | Amount per Day | Outcome Variable | Study Population | Study Length | Reference |
|---|---|---|---|---|---|
| Calcium | 400 mg | Steady state or hypercalciuria | Normal adults | 4 d | 9 |
| Calcium | 400 mg | Intestinal adaptation | Healthy adults | 4 wk | 9 |
| Calcium | 400 mg | Steady state | Adults with osteomalacia, osteoporosis, or hypercalciuria | 3 d | 10 |
| Calcium | 300 mg | Calcium retention and stabilization of PTH and $1,25\text{-}(OH)_2\text{-}D_3$ | Adult women | 2 wk | 11 |
| Chromium | <20 μg | Impaired glucose tolerance | Adult men and women | 4 wk | 12 |
| Chromium | 200 μg | Glucose and insulin | Adult men and women | 4-8 wk | 12, 13 |
| Chromium | 250 μg | Blood lipids | Adult men and women | 7 mo | 14 |
| Fats | <30 en% | Lipoprotein levels | Adults over 40 yr | 4 wk[1] | 15 |
| Fats | 40 en% | Lipoprotein levels | Adult men and women | 6 wk[2,3] | 16 |
| β-carotene | 30 mg | Carotenodermia | Healthy men | 25-42 d | 17 |
| Fish oils | 10 g MaxEPA | Stabilization of platelet and erythrocyte phospholipid fatty acids | Health adults | 3 mo | 18 |
| Fish oils | 5 g fish oil + 1 g 20:5 n-3 + 1 g 22:6 n-3 | Persistence of ω-3 fatty acids in erythrocyte membranes after discontinuation of ω-3 fatty acids | Healthy men | >18 wks[4] | 19 |

Rationale or implication:

[1]Plasma lipids, apolipoproteins, and fatty acid patterns stabilized by week 4 and remained constant thereafter through week 24.

[2]Lipoprotein levels continued to change between week 3 and week 6 of feeding.

[3]Double the turnover time of the slowest LDL component, which is about 3 weeks (20, 21).

[4]Longitudinal rather than crossover studies are advised because of the protracted washout periods (>18 wk).

Often the participant pool is larger for outpatient studies because people can go about their lives fairly normally. The nature of the study as such may dictate that outpatient studies are more suitable because people are allowed a ''more normal lifestyle.'' For this reason, the results may also be more generalizable to the population at large.

Present-day research goals do not always require a restrictive inpatient setting. Confinement to a metabolic ward is almost always a major interference with the lifestyle of the research participants; and, for some studies, it is not in the best interest of the research to disrupt the participants' daily activities and social habits. Also, inpatient studies are expensive. The high cost of human feeding studies is increasingly important to funding agencies, which are encouraging scientists to develop more efficient and cost-effective research approaches. One of these approaches is to conduct studies using free-living participants.

Outpatient nutrition studies should be considered when there is no other reason to keep subjects confined to the research unit except to provide a ''constant'' diet, when the costs of hospitalization or institutional overhead are a consideration, or when the participant is unable to reside on the unit. A combination study is often the ideal; meals are provided on an outpatient basis for most of the study and then an abbreviated inpatient phase is employed for critical data collection or testing procedures.

Outpatient studies are more difficult than inpatient studies to standardize and follow because subjects are living out of the ''controlled environment.'' To ensure compliance, some units require that all subjects eat 2 out of 3 meals per day in the research dining room, 5 to 7 days a week. This gives the participants frequent contact with the research dietitian, dietary staff, nursing staff, investigators, and other subjects and keeps motivation high. (Also see Chapter 7, ''Managing Participants and Maximizing Compliance.'')

Outpatient studies are labor intensive for the research kitchen staff because meals must be safely packed for transport, storage, and convenient reheating. Specific considerations for planning outpatient studies are listed here:

- If possible, plan a cycle menu of at least 2 to 3 days to give variety. A 1-day menu is common for short studies; however, some variety is best for outpatient studies. Longer menu cycles are generally used with longer outpatient feeding studies (see Length of Menu Cycles and Feeding Periods).
- Select foods and recipes that are easy for the research kitchen to prepare in bulk and store. Foods that are easy to prepare, freeze, store, and reheat and that are acceptable to most people include pasta with sauce (prepare and weigh pasta, sauces, and meat separately), meatloaf, Salisbury steak, hamburger patties with gravy, cookies/cakes/muffins and brownies (frozen brand names may be appropriate), rice, mashed potatoes, baked potatoes, and noodles.
- Use foods that ''travel'' well; eg, canned and frozen products. Limit the use of fresh produce because of the risk of spoilage.
- Select foods that will be readily available throughout the study. Some foods are seasonal and are available only at a high cost during off-season. For example, although fresh strawberries may be available in the market in November, they will cost too much to comply with many purchasing contracts.
- Use foods that are easy to reheat in the containers in which they are packaged; for example, mixed dishes reheat better than do whole pieces of meat. It may be necessary to purchase microwave ovens for participants who do not have them.
- Use foods that do not require multiple transfers from container to pan to dish. This may result in losses from spills or from food adhering to multiple surfaces.
- Make adjustments to accommodate routines of the various volunteers. Although dinner trays for residents may be delivered at a specified time, it may be necessary for a facility to stay open for a window of time, perhaps 4:30 PM to 6:30 PM, to accommodate work schedules of free-living adults.
- Pack take-out meals in insulated coolers with sealed, refreezable ice packs to keep foods cold during transport. On the other hand, a bag lunch for a salesperson or student may require a thermos to keep stew hot.
- Be sure the participants have adequate refrigerator and/or freezer space to store food and beverages for take-out meals. As a rule, no more than 2 to 3 days' worth of fresh food should be provided at once. Meals, snacks, and beverages for a single day often fill a grocery bag; a 2-day supply fills a large cooler. The ability to understand food storage safety should be one of the selection criteria for participants, and adequate cold storage space is fundamental to this issue.

Estimating energy requirements correctly and maintaining body weights during an outpatient study are crucial to the success of most projects. (See Chapter 17, ''Energy Needs and Weight Maintenance in Controlled Diet Studies.'') If weight maintenance is important, frequent interaction with the dietitian may be critical. This includes frequent weighing as well as monitoring of exercise patterns, sometimes daily but usually once or twice per week.

Outpatient studies require more detailed participant instruction than when participants are provided all the study food on site. ''Free foods'' and any limits on these items need to be specified. Clear, written instructions about safe food handling, storage, refrigeration, and reheating of foods should be given along with directions for handling emergency situations.

## Multiple Dietary Treatments, Multiple Calorie Levels, and Variety of Food Items

A study providing a common background diet to all participants is easier to conduct than a study with multiple dietary

treatments. Extra control measures must be implemented to avoid potential mix-ups when multiple dietary treatments are delivered concurrently. In practice, this may mean that less experienced foodservice workers could be assigned to prepare foods that will be served to all participants regardless of treatment, whereas a reliable and experienced employee might be assigned to prepare or portion foods that are vehicles for those nutrients critical to the study. There are many ways to accurately prepare and deliver multiple treatments, but they all require a high degree of organization and supervision. For example, in some facilities one employee may be assigned the task of portioning and labeling muffins of varying composition (but identical appearance) for four different diets. Another facility may prefer to have different foodservice workers portion and label each type of muffin. In both situations, records should be maintained to identify all individuals involved in the preparation and portioning of each food item so that any procedural error can be traced and corrected.

As the number of individual food items and the complexity of the items increases, more time is necessary to prepare and portion these items. Many facilities find it more efficient and less costly to purchase commercially prepared food items than to produce equivalent items. This option should be investigated within the context of the facility as well as that of the study protocol. When foods must be prepared at the facility, it is advisable to use relatively simple recipes to ensure accuracy in production. Accuracy of delivery can be improved by limiting the number of items to be distributed for a given meal. Errors of omission or duplication are easier to catch during the tray-check process when trays are not cluttered.

Although the amount of work involved in food preparation and distribution would seem to be directly related to the number of study participants being fed at a given time, this relationship is not one of direct proportion. Much of the effort of producing and portioning is in setup and cleanup rather than in cooking and weighing. There is consequently an economy of scale associated with increasing numbers of study participants—to a point. The limit of this economy of scale is reached when the burden of additional participants begins to confuse operations.

The number of participants in a study has an effect on the number of calorie levels that must be used. When each serving of food is weighed individually in proportion to energy requirements, portioning is made more complicated by greater numbers of treatments, participants, and calorie levels. In studies having few participants, the use of individually tailored calorie levels is common; the number of calorie levels to be prepared may equal the number of participants in the study. The energy requirement of each participant is assessed as accurately as possible, and daily menus are prepared to meet these calorie requirements. Typically, the kitchen staff assembles an individualized tray for each participant.

With larger numbers of participants, it is more common to use calorie increments. Menus are prepared at designated calorie levels, typically of 200-kcal to 400-kcal increments; each participant is assigned to the calorie level that most closely matches his or her estimated requirements. Participants' calorie level assignments are then changed, if necessary, to maintain their initial body weights. This method is easily used in conjunction with a modified cafeteria style of foodservice. Participants proceed down the food line selecting designated food items according to their dietary treatment and calorie level.

Menus are typically calculated at an ''average'' calorie level, then scaled so that each food item is fed in proportion to calorie requirements. This means that food items from the average calorie level are of normal serving sizes. Those at the extreme ends may look unusual; for example, a person eating foods of a low calorie level may receive many food items but less of each item than he or she is accustomed to eating. Serving unusual portions of food is a particular problem when large men and small women are included in the same study. For example, if menus are written so that small women can meet their calcium requirement, then large men may receive quantities of dairy products that they find objectionable.

Some studies have a fixed enrollment date for all volunteers. Others may have a ''rolling'' or sequential admission, in which the subjects may be engaged in different phases of the study at any given time. The latter strategy facilitates recruiting participants and has the advantage of keeping the number of participants manageable. It poses problems associated with consistency of the dietary treatments across time, however, has the potential to confound the study.

## Concurrent Studies

Extra precautions are required when multiple studies are conducted simultaneously in a facility. By coordinating activities and planning for space and equipment needs, conflicts about scarce resources can be avoided. To ensure optimal use of the facility, this extra coordination should take place among the principal investigators of the studies as well as among members of the dietary staff and should occur early in the planning process. In some facilities each study is assigned separate counter space, cooking equipment, refrigerators, freezers, serving areas, and dining areas, and little is shared except equipment. In other facilities, all studies must share all resources. This means that facility-wide quality control measures must be instituted to ensure proper delivery of test foods to the intended subjects.

Tracking expenditures for each study is more complex when more than one study is in process. The dietary staff will most likely purchase food and supplies in common for all ongoing studies and subsequently allocate costs to each study. Although this process makes bookkeeping more difficult, food costs may be lower if requirements for quantity discounts are met by combining orders.

Finally, subject morale can be affected when participants with high and low levels of study ''burden'' share a

single dining facility. It is only natural that participants in differing studies will compare their protocols for degree of effort in relation to benefits.

## Length of Menu Cycles and Feeding Periods

The decision to use a long or short menu cycle depends on a number of factors specific to the facility and the study design. However, the length of the study is a major factor in determining the length of the menu cycle. Short-term metabolic balance studies typically use menu cycles of 3 days or less. Long feeding studies generally use longer menu cycles of 1 or 2 weeks to add variety and make the diets more acceptable. The disadvantages of long cycles include the added time in menu preparation, the requirement for more labor in food handling, and a greater variability in nutrient content among menus.

Menu cycles frequently are based on 7 days, as in a 7-day or 14-day menu cycle. An advantage of this system is that certain menus can be tailored to the special requirements of carry-out meals (eg, weekend meals). These menus are often written with convenience and food safety issues in mind. Some dietitians and investigators, however, prefer menu cycles that are based on a number other than seven. This approach has the advantage of avoiding the predictability and boredom that are inherent when menus are standardized to the day of the week (eg, ''It must be Tuesday; ham sandwiches for lunch again!'')

The length of the feeding periods is selected according to estimates of how much time is needed for the outcome variable of interest to stabilize in response to a change in the nutrient variable of interest. This time period may depend on the level of the nutrient in the diet; the degree of change from the previous diet; the level of other dietary components; and characteristics of the study population, including nutritional status, age, gender, and body composition. Table 10-1 provides general estimates of the typical length of feeding periods for various nutrients and associated outcome measurements. (Note: There is seldom universal agreement on the appropriate length of feeding any particular nutrient for any outcome variable.)

## Scheduling Diet Studies

In scheduling diet studies, it is prudent to avoid holidays that might interfere with the normal feeding of participants. In the United States, this generally rules out the time period between Thanksgiving and New Year's Day. For Lent and Passover, it is sometimes possible to calculate appropriate alternate meals that will be acceptable to participants observing these holidays. Local events should be taken into account (eg, Mardi Gras in New Orleans). Dates that are likely to be important to a particular study population should be considered (eg, college breaks in a population of young women).

Seasonal effects are another factor to consider in scheduling diet studies. Nutrients in specific foods can change with the season (an example is the carotenoid and vitamin C content of summer vs winter tomatoes). Outcome variables may be affected by colds and flu, which are common in winter, or by allergies, which are commonly induced in spring and fall by pollen. The summer months are problematic for conducting feeding studies because of changes in physical activity and conflicts with vacations. Unwelcome snow storms may interrupt diet studies at critical points of dietary intake and sample collection. Elderly subjects may be less interested in studies conducted in winter months because of anticipation of poor driving conditions and the safety issues that accompany shortened daylight hours.

## Tailoring the Study to the Physical Facility

Architectural plans for a metabolic research kitchen must address a variety of special needs. Ideally, these include cooking facilities that allow for multiple modes of preparation; workstations that are efficient and well equipped for weighing, packaging, and preparing food; storage space for refrigerated, frozen, and dry goods; and dishwashing facilities. Office space, including computer workstations for dietitians and technicians, as well as a dining room for outpatients, may also be included. A setting that provides for all of these needs can successfully accommodate multiple studies and large numbers of subjects consuming complex diets for long periods of time either at the facility or as outpatients.

Rarely, however, is this ideal setting available. Usually the study must be tailored to an existing physical facility. (Also see Chapter 19, ''Facilities and Equipment for the Research Kitchen.'')

Because space restrictions lead to equipment limitations, frequently only one piece of each type of equipment is available. Consequently, contingency plans must be available at all times to provide for emergency situations such as breakdowns, repairs, and replacement of equipment. Most research kitchens that do on-site cooking should have both a conventional range/oven and a microwave oven. A double-oven household range can provide assurance that if one oven breaks down, the other will still be in working order. If a microwave oven breaks down, the range and oven can provide a method of reheating. A portable hotplate can also serve this purpose. If a dishwasher is out of order, paper supplies should be readily available for meal service. Most institutions are required by their state public health department to meet sanitation codes governing dish washing and do not allow washing dishes by hand without a disinfectant. Alternative refrigeration and freezer space should be identified for emergency food storage when such equipment fails. Ideally, important refrigerators and freezers will be connected to an emergency generator.

To conduct successful feeding studies under circumstances of limited storage space, it may be necessary to study fewer participants at a time, to extend the study over a longer time period, and to offer fewer food choices. As long as sufficient quantities of key food items can be stored for the participant at any given time, intrasubject variability in nutrient intake over long periods of time can be minimized. In addition, chemical analysis of diet composites can provide a measure of variability in nutrient intake across time.

Meals may also be simplified so that only those foods containing key nutrients are kept in storage. Other food items may then be procured as needed. For example, in a study investigating the effects of vitamin C on the incidence of colds, the diet can be designed so that frozen orange juice is the only significant source of vitamin C in the diet. Frozen orange juice would then be purchased in a single lot shipment and would be the only food needing storage for the length of the study. The remainder of the diet, composed of foods low in vitamin C, could be replenished on a regular basis.

Food procurement, preparation, storage, and delivery from another foodservice department within the institution can decrease storage needs and reduce on-site food production. This arrangement can be particularly helpful if cooking facilities and personnel are limited. Under these circumstances diets might be designed around portion-controlled, precooked items that may even be available as frozen entrees and preportioned foods such as juice, cereals, and snacks. It is necessary, however, to evaluate in advance whether the composition and weight of such food items are sufficiently accurate and constant for the purposes of the study.

This approach has been effectively used by McCullough et al (22) in studying electrolyte balance. Inpatients consuming rigorously controlled constant diets were compared to outpatients consuming less exactingly controlled diets consisting of manufacturers' preportioned foods and other foods prepared and weighed in the hospital's central food production area. Analyzed diet composition for electrolytes and for 24-hour urine collections showed no statistical difference between the two methods of dietary control.

The number of employees that can effectively and efficiently work in a given work area is likewise governed by the amount of space and equipment available. Simplifying the meals, food selections, and meal rotations can decrease the number of food items that need weighing and preparation. This can decrease personnel requirements. The maximum capacity for the types and numbers of research diets produced should be established in advance. Creative staffing patterns, sometimes extending into the late evening, can address the problems of space limitations and increased production needs. The use of temporary personnel can also effectively meet the study's needs for short periods of time.

The efficiency of a research kitchen is maximized in studies that supply food for home consumption because the meals do not have to be prepared and served three times a day. Food pickups by the participants can be arranged for both morning and afternoon to free up refrigeration space. Once the morning food is picked up, refrigeration space then becomes available for the delivery and storage of food for the afternoon or evening pickups. To use a work schedule of this kind, perishable foods and some precooked foods may need to be procured from another foodservice area and brought to the unit on a meal-by-meal basis. These arrangements can frequently be made through the institution's food services.

Ultimately, the limitations of space, equipment, and personnel within a research kitchen must be addressed individually with emphasis on the ability to maintain accuracy of food preparation and service and continuity of function by a trained staff. Careful consideration of the necessary dietary controls will address most scientific and logistical issues in advance. Often, food preparation procedures can be simplified, resulting in improved efficiency and accuracy. With thoughtful creativity and advance planning, well-controlled feeding studies can be conducted in almost any facility.

## Pilot Studies

A *pilot study* is a small-scale study that is conducted to facilitate the successful completion of a full-scale study. The many reasons for conducting pilot studies include: gathering preliminary information prior to committing scarce resources; assessing the feasibility of a feeding regimen; and honing techniques for the analysis, storage, and distribution of foods and samples. Pilot studies also are used to refine protocols as well as to make comparisons and choose among alternative approaches.

It is important that treatments, subject populations, and study conditions used in a pilot study closely parallel those planned for the subsequent, full-scale study. Investigators must resist the tendency to use inadequate dietary control groups or treatments; controls are as essential for interpreting the results of a pilot study as they are for interpreting a full-scale study. In addition, the subjects participating in a pilot study should resemble those who will participate in the subsequent, full-scale study; otherwise, the data gathered may be misleading. For example, procedures and menus planned for a study in elderly individuals should be pilot-tested on persons from that age group, not on young students or middle-aged adults.

For the dietary staff, recipe development is an important aspect of pilot studies. Some recipes that initially appear to be successful may not hold up under the close scrutiny of a pilot study. During recipe development, the food is taste-tested for quality and acceptability with several people eating a whole portion as part of a meal. Tasting a spoonful is often not enough; eating the same amount that the participants are expected to consume can lead to a different evaluation of the food item. Portions of the recipe are stored as the food item will be for the study (refrigerated/frozen) and reheated at a later date to evaluate how these treatments affect appearance and quality of the product. Any changes that are made to the recipe are incorporated, and the evaluation process is repeated.

To test for potential problems associated with scaling for quantity preparation, the recipe is made in amounts that will ultimately be used for the study. All procedures and details of preparing the recipe are documented. The insights of kitchen staff can be tapped to assess the ease of preparation, availability of foodstuffs, and other pertinent considerations.

In preparation for the pilot study, the kitchen staff, nursing staff, laboratory staff, and study coordinator develop study-specific flow sheets, ordering forms, and quality control guidelines. (See Chapter 3, ''Computer Applications in Controlled Diet Studies,'' and Chapter 18, ''Documentation, Record Keeping, and Recipes,'' for examples of forms.) As with a full-scale study, a statistician should be included on the research team.

With these steps completed, the pilot study can begin. At this time, many aspects of the study can be fine-tuned, comments collected, and data gathered. Besides cooking and tasting recipes, serving the food, and checking the composition of menus, many other activities and procedures can be pilot-tested. These include all laboratory analytical techniques, sample processing and storage procedures, record-keeping procedures, forms, interviewing techniques, recruitment strategies, nursing techniques such as blood pressure measurements, and data processing. Pilot studies can be extremely useful, not only because many preliminary discoveries are made at this step, but also because the design, diet plan, or procedures can be ameliorated before sponsors invest effort and money on a larger scale study.

A final evaluation of the pilot study is done at this stage and plans are revised. If enough participants were studied and the outcome variables were measured after a time course similar to the one planned for the major study, data collected during the pilot study may be used by the study's statistician in a power analysis. This calculation can provide valuable data to project the number of participants that will be required for the full-scale study in order to determine statistically significant differences among treatments.

There are many advantages to conducting a pilot study:

- Data collected is likely to predict the success of a full-scale study.
- Rough spots and failures in the recruitment process, in the kitchen, and in the research laboratory can be corrected prior to outlay of major resources.
- New staff members can be trained under less pressure than during the full-scale study.
- Recruitment strategies for subjects can be improved.
- Recipes and menus can be improved based on input from study participants and kitchen staff.
- Sample handling and techniques for laboratory analysis can be evaluated.
- Foods can be composited and chemically analyzed to predict accuracy of nutrient content for the full-scale study.
- The number of persons, the time commitment, and the cost required to carry out the full-scale study are more easily predictable.
- Data from the pilot study can be used in a power calculation to estimate the number of subjects required in the full-scale study.
- Data from pilot studies will often convince a funding agency to support a major study. Data from pilot studies are often publishable.

## Estimating the Cost of Diet Studies

Producing research diets is an expensive endeavor—so much so that their cost is a major consideration in the design and implementation of human feeding studies. Injudicious cost-cutting maneuvers, however, can jeopardize the integrity of a study. The research dietitian thus walks a fine line in an effort to contain expenses while committing the resources required to achieve the primary goal of producing high-quality diets of specified composition.

Various feeding patterns have been successfully used in research studies, depending on the level of control required, the facility, and the research question to be addressed. As shown in Table 10-2, studies that require a high degree of dietary control usually are more expensive. Such studies typically require longer hours of facility operation, more supervision of research participants, and more personnel, all adding to the cost of conducting a study. The goal is to provide the degree of dietary control required for a particular research question without spending additional resources when control is not required.

Liquid formula diets probably are the most cost-effective of all the research diets. However, ingredients, even when purchased in large quantities, are still expensive. The food costs for some liquid formula diets may match the food cost of a natural food diet, but the labor cost likely will be much lower. For example, in a typical facility an employee can prepare 80 liters of a single formula each day that supplies 64,000 kcal. This is enough to feed a participant for a month, and there is little waste.

The cost of producing research diets varies among studies and among facilities but is based, in large part, on the complexity of the study, including level of labor; number of meals served and hours of facility operation; the type of diet, including the expense of dietary components; the nature of the measurements made on participants; and payments and other charges associated with enrolling study participants.

### *Labor*

Labor is the major operating expense for most feeding facilities. A major responsibility of the research dietitian is to assess, within the framework of each new study, the skills and the time requirements of each position and to make assignments accordingly. Additional employees frequently are needed for days or hours of peak workload; it can be less expensive to make appropriate use of part-time and overtime labor than to hire additional full-time employees. Some fa-

**TABLE 10-2**

**Direct Relationship between Degree of Dietary Control and Expense of Conducting a Study**

| Level of Dietary Control | Cost | Features |
|---|---|---|
| Highest | Highest | • Metabolic ward<br>• Formula and conventional food diets<br>• All meals supervised<br>• No alcohol<br>• All foods analyzed for selected nutrients (23) |
| High | High | • Free-living participants<br>• Conventional foods<br>• Two supervised meals Monday–Friday<br>• Lunch and weekend meals packed for take-out<br>• No alcohol<br>• Diet composites analyzed for selected nutrients (24) |
| Medium | Medium | • Free-living participants<br>• Conventional foods<br>• Two supervised meals Monday–Friday<br>• Two self-selected weekend meals (within guidelines)<br>• Alcohol consumption allowed within limits<br>• Diet composites analyzed for selected nutrients (25) |
| Medium | Low | • Free-living participants<br>• Self-selected diets<br>• Food records<br>• Fiber-rich cereals prepackaged for home consumption (26) |
| Low | Lowest | • Free-living participants<br>• Self-selected diets based on flexible, individualized diet plan<br>• Food records<br>• Food frequency questionnaire<br>• Diet counseling (27, 28) |

cilities successfully employ students, especially college-level dietetic or foodservice management majors, or secondary school students who are enrolled in work training programs. The personnel department can provide advice about institutional regulations and liabilities regarding the use of students and volunteers in the research kitchen. In some settings the kitchen staff may be hired only in accord with strict union contract rules.

It often is advisable to plan the staffing budget on a year-round basis even if the study participants are actively engaged in the feeding protocol for only part of the year. This recommendation acknowledges the complete time sequence of the research protocol. For example, before the study begins the nutrition staff must be trained and must try out the experimental menus to ensure they meet the study design goals. There is a great deal of preparation work before and between feeding periods. Also, if the investigation comprises a series of studies, it is inefficient to lay off the trained staff and hire new recruits a few months later. Studies are not part of the usual hospital foodservice activity, and highly skilled, well-motivated workers are needed to ensure that the protocols are being followed correctly.

In some facilities, free-living participants perform limited but time-saving functions as part of the study protocol. For example, labor hours are saved by having participants rather than staff members assemble the items required for a take-out lunch: participants can collect their lunch items along with breakfast items as they progress along a cafeteria line, then pack lunch items for take-out. The time required for a staff member to check the accuracy of participants' selections can be considerably less than the time required for a staff member to assemble the trays. This must be done without burdening the participants and without breaking the blinding of the study. (Also see Chapter 20, ''Staffing Needs for Research Diet Studies.'')

## *Purchasing Food and Supplies*

### *Food*

The research dietitian must view food selection and purchasing within the context of three major goals: (1) to control nutrient content of the diets, (2) to aim for participant compliance, and (3) to follow principles of cost containment within the parameters of the research protocol. This means

that food costs will vary considerably among studies, depending on the design. Ingredients for a simple formula diet may cost as little as $5 per day, whereas the components for constructing whole-food diets with specially manufactured ingredients may cost as much as $20 per day. The decision to purchase a brand-name cookie at a higher price than a nonbrand-name counterpart may be justified if it promotes compliance or if nutrients are more consistent among lots. Similarly, a particular brand of reduced-sodium and reduced-fat salad dressing may best suit the requirements of the researcher and the palates of the participants.

To minimize waste and save money, the dietitian must order each food in the quantities needed. This is no simple task, because each food item must be assessed separately considering its rate of use, shelf-life, and stability once opened. Additionally, greater waste is associated with weighed food portions. For example, when a hard roll or bagel is portioned and precisely weighed, a large part may be lost to maintain the aesthetic appeal of the served portion.

Buying in large quantities of single batch lots not only ensures consistency in nutrient composition for the entirety of the study but also has the benefit of discounted prices if the supplier's required minimum order is met. Although purchasing in bulk can be cost-effective, it is not appropriate in all situations. For example, when a recipe calls for 10 g more than is supplied in an institutional pack of tuna, it is cost-effective to stock small cans as well. The amount of storage space available also influences whether items are purchased in bulk. If storage space is limited, additional emphasis will be placed on selecting a food item that is readily available and provides consistency of nutrients across lots.

Buying in bulk is an appropriate method of purchasing ingredients for liquid formula diets. However, special consideration must be given to the shelf stability of the ingredients, including the fat and protein sources, which may deteriorate over time. This is particularly important for dried milk powders and other ingredients that undergo Maillard (browning) reactions and other changes affecting taste.

Storage represents another food-associated cost in diet studies. Bulk dry storage at room temperature requires large amounts of floor space, usually in locked rooms; the institution where the study is conducted may charge for this space. Walk-in refrigerators and freezers may be needed. It also may be necessary to rent space for bulk frozen or refrigerated items in specialty warehouses. These facilities usually are located at a distance from the research center. Beyond the rental fees, additional travel and time costs are incurred when staff go to refrigeration sites to retrieve the food.

In deciding whether to make a food product ''from scratch'' or to purchase a commercially available product, considerations for controlling nutrient content of diets override principles of cost containment. However, in some cases commercially available foods can be used appropriately and offer a cost savings compared to food and labor expenses incurred with the in-house production of a comparable product.

It is wise to allot funds for food composition analysis both before the study (during validation and pilot phases) and during the conduct of the protocol (monitoring phase). The cost of chemically analyzing a commercially prepared mixed dish such as baked lasagna may be less expensive than the labor involved in preparing the dish. Many commercially prepared mixed dishes are highly standardized and companies typically provide nutrient analysis of the product. (Some food companies are willing to share available nutrient data that is not included on their nutrient data sheets.) However, it is important to determine the variation among portions of commercially prepared dishes; within-batch or among-batch variation may be unacceptably high.

### *Supplies and Materials*

Just a generation ago, the term *paper supplies* referred largely to paper napkins and cups, waxed paper, and aluminum foil. Today supplies include a substantial proportion of Styrofoam, plastic wrap, and other disposable containers and utensils. Although the cost of paper supplies varies among facilities, as rule-of-thumb estimate, the expense of paper supplies is approximately 10% of food costs.

Disposable plastic and paper containers have become a mainstay in the preparation and service of research diets. Frequently, foods are weighed in advance of the study, portioned into high-quality disposable containers, frozen until ready for use, and then assembled on permanent ware for service in the hospital setting or kept in the original container when a packed meal is ordered. Food needing to be reheated prior to service can be microwaved in these same containers if plastic or paper is used.

Although disposable containers are convenient, a high price is paid for their purchase and disposal. Disposing of solid waste will be an increasing concern for foodservice managers as disposal costs accelerate. Studies are needed to document the amount and type of solid waste generated in feeding facilities.

## *Budget Planning for Research Diet Studies*

As earlier discussions make clear, feeding studies create some unique budgetary pressures that other types of research are spared. Although categories vary according to institutional policies, the general categories that must be considered when researchers develop the study budget are:

Personnel (includes salaries, wages, overtime, and fringe benefits)
- Principal investigator
- Coprincipal investigator
- Research dietitian
- Medical officer
- Study coordinator
- Secretary/administrative support
- Cooks
- Foodservice workers
- Nursing support
- Laboratory technicians
- Phlebotomist

- Statistician
- Consultants

Administrative Expenses
- Travel (out-of-town meetings, local mileage)
- Telephone/other communication
- Publications
- Shipping
- Postage
- Office supplies
- Facilities charges
- Nutrient database software
- Printing and photocopying

Foodservice Expenses
- Food
- Paper goods and disposables
- Kitchen supplies, equipment, and maintenance
- Coolers/cold packs
- Off-site freezer/refrigerator storage
- Laundry, linens, and uniforms

Laboratory Expenses
- Equipment
- Clinical laboratory tests
- Laboratory supplies
- Diet composite analysis
- Service contracts on laboratory equipment
- Blood collection and processing supplies
- Sample storage

Subject Costs
- Subject payment
- Recruitment costs/advertising
- Parking fees/public transportation/local mileage

The exact assignment of these costs to specific categories (for example, is food a ''supply'' cost or does it fall under ''other'' costs?) will vary among research centers, depending on factors such as the policies of the funding agency and the budget format preferred by the institution.

The financial structure of studies differs among research centers. For example, the nature of institutional support varies considerably: some investigators may need to request funds for nursing services that elsewhere may be provided without charge. Another highly variable factor is the indirect cost or overhead rate. In some situations this is minimal (ie, 10%), whereas in others it can be high enough (ie, 80%) to effectively double the cost of the project.

Costs may be calculated on a per-study, per-subject, per-meal, or per-annum basis. This basis will vary with the category:

- Small equipment (such as kitchen scales) is usually purchased once at the outset of the study.
- Financial compensation or stipends would be paid in fixed amount to each participant.
- Parking fees may be charged each time the participant drives to the center for a meal.
- Salary support for a principal investigator usually represents a percentage of full-time effort per year.

Although it may seem that costs in all categories would be proportional to the number of participants enrolled, this is not the case. Any study, regardless of size, requires a certain minimal number of staff; increments about this, however, may be irregular. The necessary level of labor for dietetic and kitchen staff is particularly high; it tends to range from 0.2 to 0.5 full-time equivalents (FTE) per participant, depending on the complexity of the protocol. In addition to the nutrition personnel, scientific, medical, statistical, managerial, and laboratory effort is needed; when summed, this effort can vary from 2 FTE to 6 FTE.

Study subjects often receive a stipend or financial compensation for participating in the study. This is a common, but not universal, practice. Some investigators believe that a financial incentive is a disservice to participants because it can pressure them to continue with a study when they prefer to withdraw. This consideration is compounded when payment is partially or fully linked with completing the study. Others believe that the study will be taken more seriously when there is payment involved and that this incentive promotes compliance and willingness to complete long studies. Offering a financial incentive also can broaden the recruitment pool, which is often an important consideration when participants with specific characteristics are being sought. (See Chapter 5, ''Ethical Considerations in Dietary Studies,'' for further discussion of stipends.)

## Conclusion

Controlled human feeding studies are labor intensive, expensive, and require a great deal of attention to numerous details, but they can yield information that cannot be gained by other types of research. Advance planning for all aspects of human feeding studies can lead to cost savings, greater accuracy in data collection, and a more harmonious setting for study participants as well as dietary and research staff.

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