PART 2

Human Factors

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CHAPTER 5

ETHICAL CONSIDERATIONS IN DIETARY STUDIES

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The principal investigator and coinvestigators are responsible for the welfare of participants and staff before and during the study, and for a limited time after its completion. This is the guiding principle for all plans and decisions concerning the design and conduct of human studies so that they are ethical and safe. Institutional safeguards and professionalism work together to ensure that studies involving human subjects are ethical and safe, that informed consent is obtained, that data collection and reporting of results follow approved written guidelines (eg, the protocol), that participant confidentiality and privacy are strictly maintained, and that conflicts of interest are avoided. The primary institutional structure supporting these efforts is the institutional review board (IRB). The IRB is the authorized body having oversight over study protocols and other aspects of human research activity, and gives assurances to funding agencies and other parties that research involving humans complies with federal regulations for the protection of human research subjects.

Professional organizations support ethical conduct by developing and promoting codes of ethics to their members. Safety monitoring committees and external bodies such as data and safety monitoring boards may also be used, mainly in large studies or studies in which the well-being of human subjects must be safeguarded.

Issues of ethics and safety can arise at any step of a human feeding study. By anticipating and developing plans and procedures in advance, unethical situations can be avoided. (Note: Many of the considerations outlined in this chapter will not apply to all studies in all research settings.)

PLANNING THE STUDY

Study Design

When researchers design a study, it is generally desirable to maximize the difference in independent variables to ensure that the study will detect an effect, but the magnitude of the difference often must be tempered in human studies to protect the welfare of study participants. In contrast to animal studies, which may be designed to produce an unhealthy outcome (eg, a deficiency or excess of dietary components), human studies should leave the study participants in no worse health than when they entered the study. Study designs that could produce a potentially adverse biochemical or physiological effect should also offer the participants a post-study corrective period. For example, in a 6-month research study conducted on obese women, the design required par-

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ticipants to maintain their body weights. Because obesity is a health risk, the obese women were required to obtain permission from their physicians to remain obese for that 6-month period. Immediately following the study, these women were provided with weight-reduction counseling (1). In addition, if the correction is included in the research design, more can be learned about the effect being studied.

Three main factors related to participant burden and research risk should be considered when investigators design a study: (1) invasiveness of the specific procedures, (2) malaise, and (3) excessive burden caused by too many measurements, activities, or restrictions.

During the planning phase, investigators must carefully consider the need for invasive procedures and particularly the amount of blood that will be collected. Because studies are expensive, there is a tendency to assess as many outcome variables as possible, which may require drawing a large amount of blood. Although this issue is carefully reviewed by IRBs, it is the investigator's responsibility in planning a study to be even more fastidious than the IRB requirements demand. Investigators often find it difficult, however, to truly appreciate the invasiveness of a procedure purely through ''thinking.'' It thus is wise (when feasible) for investigators to experience the contemplated procedures and also the entire measurement protocol. This helps in making modifications that not only preserve participant well-being but also aid in recruitment and in encouragement of participants once the study has started. Investigators who can honestly say that they have gone through the procedures and have found them tolerable will engender trust and protocol adherence.

In addition to experiencing and understanding the degree of invasiveness, the primary investigator who goes through the entire measurement protocol can also experience the potential overall malaise produced by the procedures. For example, investigators participated in a pilot study designed to assess the absorption and metabolism of β-carotene (2). A small butterfly needle was inserted into a vein in the hand and, after each blood draw, a small amount of heparin-saline solution was injected to keep the blood from clotting in the line (ie, a heparin lock). Blood was taken for 8 hourly draws but the investigators went on with day-to-day work. Although the investigators found the procedures to be quite tolerable that day, the next day they all experienced a small degree of malaise (ie, they were able to work but were not their most productive). In this example, the question of ethics is: how many times in the course of a study must a study participant experience malaise? Investigators who are aware of this effect can make every effort to minimize these occurrences and can point out to potential participants that they may experience days or times of reduced productivity and vitality. When students are participants, it is important to be aware of when they need to be performing at their best (ie, during examinations) and avoid scheduling such collections at those times.

When planning studies, investigators must be aware of the total participant burden. It is easy to make increasing requests of participants either as part of the original study plan or as interesting issues arise during the course of the study. These requests may seem fairly benign on an individual basis; for example, asking subjects to fill out a daily activity sheet, weigh themselves each day and plot their weight, mark down how many snacks they consumed, and fill out a form for each take-out meal. Many of these demands may not be specified in the original informed consent document but are involved in the day-to-day quality control of the study. The sum of the requests, however, can produce an overwhelming participant burden. Symptoms of burden appear as partial responses, sloppy forms, forgetting about forms, and need for constant reminding by staff. It sets up an unhappy study atmosphere for both the participants and the staff, who often are not the ones who decided to manage the study by ''filling out forms.'' The burden to the participant can be minimized by eliminating all but the most necessary data collection and management forms and by having the staff take up as much of this burden as possible. If extra forms are required, the investigator must explain this to all the participants and may need to obtain their consent to the additions.

Principal Investigators

Some investigators avoid human studies in the belief that only physicians should be principally responsible for the welfare of participants. However, many of the classical nutrition studies of healthy individuals have been led by investigators with other doctoral degrees (ie, PhDs). In clinical studies involving patients who suffer from a specific disease, principal investigators may need to be physicians because of the chance that study conditions will compromise the health of the participants. Alternatively, physicians may be named as coinvestigators and directly participate in the study, or they may be named as consultants and provide advice as needed. Regardless of medical background, the principal investigator must be willing to take full responsibility for the welfare of the participants. The main organizational structure that provides principal investigators with guidance and oversight is the IRB. Other organizational structures include safety monitoring committees, independent data and safety monitoring boards, and professional organizations' codes of ethics.

Institutional Review Boards

Each institution, whether hospital, clinic, university, or other research organization, must have its own IRB to review each study protocol and the language of the informed consent document for the propriety of the approach, the physical and psychological safety issues, and the possible risks and benefits to participants. No recruitment of participants or advertisement of the study may commence before IRB approval is obtained. Studies may require the participation of more than one institution. For example, university-based investigators and graduate students may be conducting the study, but one of the measurements or procedures must be carried out in a hospital or clinic facility. IRB approval is usually

necessary from both institutions, which often means filling out two completely different sets of forms. Requests for funding from federal sources, trade organizations, or foundations also require IRB approval of protocols before the study is funded.

In order to meet deadlines for grant applications, institutions with experience in grant applications may issue a ''pending IRB'' document once the application has been submitted to the IRB committee.

In this situation it is anticipated that the investigator's IRB application will be approved during the time period that the grant proposal is under review by the funding agency. This permits the review process to go forward, but funds are withheld until the agency receives documented proof of final IRB approval.

IRBs vary in their operating procedures, in the forms they require, and in the time it takes to grant approval. IRBs also vary in their willingness to allow research studies of various types. It is worthwhile for researchers to learn, in advance, the usual concerns of IRBs and to address them in the protocol. Because IRBs may meet monthly, a month should be allowed for approval and another period of time allowed to answer any questions or concerns of the IRB. Such concerns and requests for changes often relate to the informed consent documents.

In the federal government the Office for Protection from Research Risks (OPRR) is an administrative unit within the Department of Health and Human Services (DHHS). OPPR is organizationally located at the Office of the Director, National Institutes of Health (NIH). The main responsibility of the OPPR is to implement DHHS Regulations for the Protection of Human Subjects (45 CFR 46) and to provide guidance on ethical issues in biomedical or behavioral research (3). In order for human research to be funded by NIH, the research institution must provide written assurance of compliance with DHHS regulations. In addition, the principal investigator must provide evidence that the proposed research has been approved by his or her institution's IRB.

Other Oversight Committees and Guidelines

Oversight committees and professional guidelines assist principal investigators in planning and conducting studies that are ethical and safe.

Safety Monitoring Committee

To ensure the impartial monitoring of participant welfare, longer human studies can benefit from the expertise of a safety monitoring committee. If the principal investigator is not a physician, it is important for the committee to be partially composed of physicians with training appropriate to the evaluation of health effects that study participants might experience. Committees composed of two to four physicians, at least one of whom is actively engaged in research, can effectively oversee the ethical and safe conduct of a study. This committee may or may not be the same as the oversight committee that may be required for IRB approval of the study.

The chairman of the safety monitoring committee should be empowered to call meetings of the committee at any time with or without the attendance of the study investigators. The major objectives of an oversight or safety monitoring committee are to: (1) review the study protocol for ethical issues and safety, including policies for referrals to health care providers; (2) review the health status of prospective participants in order to protect their interests with regard to participation in the study; and (3) be ''on call'' for questions concerning ethics and safety during the study.

Investigators can facilitate the performance of the safety monitoring committee by appointing the committee early enough so that substantive protocol changes can be made if necessary. The safety monitoring committee reviews written procedures that specify under what conditions participants should be referred to their own physician or other health care provider for evaluation. The safety monitoring committee also may help evaluate the health status of prospective participants. The principal investigator can assist the committee in this process by providing physical examination information, laboratory values, and screening information about each of the potential participants, and pointing out any particular concerns.

It is rare for all potential participants to have all laboratory values within the normal range, and sometimes other issues arise. When participants are older or have a particular disorder, such as high blood pressure or raised serum cholesterol concentrations, usually a decision must be made about whether the study protocol will in any way jeopardize the potential participants' well-being. In order to have this information available for the safety monitoring committee, investigators should plan for an adequate recruitment and screening period. The more exclusion criteria there are, the greater the difficulty of recruitment and screening. The safety monitoring committee provides an important restraint against the tendency to justify the acceptance of participants into the study in order to meet recruitment goals, especially when finding eligible participants is difficult.

The safety monitoring committee is also helpful in providing advice concerning decisions that must be made during the study. For example, four months into a study to assess the lipid response of premenopausal women to the American Heart Association Diet (30% of energy from total fat, with a polyunsaturated to saturated fat ratio of 1.0) a participant suffered a gall bladder attack and had her gall bladder removed. She was sure that the diet had caused her attack and demanded that investigators pay the hospital expenses, which were not included in the tight budget for the study. The safety monitoring committee decided that the diet was highly unlikely to be the cause of her attack. The informed consent document, which was signed by this participant, clearly stated that the investigators or the university could not be held responsible for health problems not related to

study participation, so she was not paid for hospital costs. It would have been difficult to come to this decision without the committee's involvement. The committee also recommended that for future studies investigators screen out all potential participants who could not document their health insurance coverage. However, this could cause the loss of a large pool of participants, greatly limiting the generalizability of the findings and restricting equal access to the benefits of research.

Data and Safety Monitoring Boards

For larger studies, especially multicenter ones, formal and independent data and safety monitoring boards may be appointed, often by the funding agency, to serve as an oversight committee. To guard against conflicts of interest, the members of this board should generally not be affiliated with the institutions of any of the investigators.

The role of the data and safety monitoring board is to monitor, review, and assess the progress of the study. The data and safety monitoring board has access to unblinded outcome data during the study and has the responsibility to ensure that participants are not exposed to unreasonable or unnecessary research risks. Toward this aim, the data and safety monitoring board may recommend early termination of a study if the data suggest significant adverse risk to study participants or if the research questions and objectives appear to have been answered and therefore participants should not continue to be exposed to risk. The data and safety monitoring board also monitors recruitment progress and reviews the quality of the data.

Professional Code of Ethics

Professional associations support ethical conduct by developing and enforcing codes of ethics relevant to their professions. For dietitians, the relevant code of ethics is The American Dietetic Association Code of Ethics for the Profession of Dietetics (4), which sets forth professional principles and standards of conduct. The code is important for guidance of professional activity and strengthens the credibility and integrity of the profession.

Obtaining IRB Approval

Informed Consent

Under the 1974 Federal Act for Research with Human Subjects (5), the concept of informed consent was developed as a guiding principal for the ethical conduct of human research. Since then, commissions have been established and regulations revised and/or expanded (3, 6). The main principle of the act was that potential study participants were free to consent to study participation as long as they were informed of all the study requirements, risks, and benefits.

Certain groups were identified as less able to give informed consent. Among these were children, the mentally ill or retarded persons, and prisoners. These classes of individuals can participate in research studies if a legal guardian gives informed consent for their participation. (Students may also fall into this category if the situation is coercive, such as when study participation is required to obtain a passing grade.) Although the original policy legally applied only to federally funded research, many states have enacted their own statutes.

To implement this policy, study participants are required to sign an informed consent document that clearly describes the requirements of the study in language that can be easily understood. The study participant must sign the document before entering the study.

Each institution has different requirements for the format of the official informed consent document, but the basic intention among documents is similar. The document must describe, in detail and in language that the prospective participant can understand, all that will be expected of him or her in the research project. For complex protocols such as a feeding study, the day-to-day expectations for study management (such as filling out a daily well-being form, taking shoes off and being weighed each day, signing a log book for take-out meals, attending to meal serving times, and scheduling of appointments for measurements) cannot be explained in a concise enough fashion for the informed consent document. All the particulars of a study need not be included in this document but should be orally explained (sometimes with the help of written materials) to potential participants at one or more meetings. In this case the informed consent document would concisely describe the basic requirements of the study. Exhibit 5–1 provides an example of an informed consent document.

It is useful to make a checklist of handouts, descriptions, and caveats for the study manager or recruitment interviewer to discuss with the participants. Because the study manager talks to a number of potential participants over a period of time, the checklist for each participant is checked off as each item is discussed, and the participant signs this checklist to assert that each item has indeed been described to his or her satisfaction. Exhibit 5–2 is an example of such a checklist. Note that the checklist can be used to document whether participants have seen these criteria. Participants are given a copy of the checklist along with their informed consent document.

Informed consent documents must always state that the participant, being a volunteer, has the right to withdraw from the study without fear of any retribution and that withdrawal will not affect the participant's standard medical care. However, it may also be important to note in the informed consent document that the participant may be terminated from the study. Such a step becomes necessary if a participant displays abusive or highly emotional behavior, which may occur in feeding studies because of the combination of highly restrictive protocol requirements and a lengthy study period. Criteria that specify behaviors that would precipitate participant termination are listed in Exhibit 5–3. This form can be incorporated into the informed consent documents or presented to participants after they are enrolled.

EXHIBIT 5-1

Example of Informed Consent Document for Adults

UNIVERSITY OF ILLINOIS AT CHICAGO
INSTITUTIONAL REVIEW BOARD
ADULT CONSENT FOR PARTICIPATION IN AN EXPERIMENTAL PROJECT

Please complete the following statements in the first person and in lay language.

1. I, _____, state that I am _____ years of age and I wish to participate in a program of medical research being conducted by: _____ (investigator).
2. The purpose of the research is: to determine the effects of dietary modification consistent with the recommendations in the American Heart Association Phase Diets (AHA Diet), namely reduced total fat and cholesterol intake along with altered polyunsaturated fatty acid (PUFA) to saturated fatty acid (SFA) ratio, on various lipid parameters, nonlipid atherogenic parameters, and other parameters that may be influenced by such dietary measures. The effects of dietary soluble fibers will also be explored.
3. The experimental procedures are:
   a. Consume only the foods provided in the Metabolic Unit (two regimens: high-fat (40%) diet for one month and low-fat (20% or 30%) diet for next months) over a period of 6 months. In case of a need, packed meals will be given to eat outside the site. The study runs from January through June. The major holiday during this time is Easter. We will make arrangements for you to take packed meals for this day or Passover or other special holidays. It will not be possible for you to leave the campus for more than 1 day at a time. This means that spring break and the remainder of the month of June after classes are finished must be spent on campus.
   b. Provide blood samples at regular intervals as specified below: 2.7 oz on days 22, 29, 67, 141, and 169 during the 6-month study period; 1.34 oz on days 1, 85 and 113 during the 6-month study period; .34 oz on the eighth and eighteenth days of each menstrual period during the study; 1.9 oz on a day in the fourth week and again in the twenty-fourth week for the post-prandial testing.
   c. Provide adipose tissue biopsy samples on days 29 and 169 of the study period (a physician will take these samples).
   d. Subject to underwater weighing once in the fourth and again in the twenty-fourth week.
   e. Provide complete fecal and urine collections from day 20 through 24, day 50 through 56, and again from day 129 through 133.
   f. Keep records of physical activity for 5 days during the months of January, April, and June.
4. The personal risks involved are (if none, so state): Essentially, none. The diets are those advocated by the American Heart Association, National Cancer Institute; and Dietary Guidelines for Americans. No adverse effect is expected. A small bruise as a result of pricking for blood drawing or adipose tissue biopsy may be evident for a while. Trained phlebotomists and physicians will be performing these tasks; hence bruising will be minimal. Participation in a diet study may be very stressful because of change in lifestyle. These stresses have been discussed with me in this interview.
5. I understand that I will receive standard medical care, if required, even if I do not participate in this study. Alternative procedure and therapy that might benefit me personally are: Not applicable because all are healthy adults.
5. I understand and accept the following research related costs (this refers to costs which are beyond those required for my normal diagnostic and treatment purposes). If no additional research costs are to be paid by the employee/volunteer state NONE.

   NONE
7. I understand that I will be paid $5/day (168 days = $840 in installments: $100 to be paid after each of the following sessions of blood drawing—days 28, 56, 84, 112, and 140 (total $500). The remaining $340 will be paid on day 168. These payments will be made in compensation for the time and attention I give the project.

Continued

EXHIBIT 5-1

8. COMPENSATION STATEMENT (Check appropriate statement).

☐ I understand that in the event of physical injury resulting from this research there is no compensation and/or payment for medical treatment from the University of Illinois at Chicago for such injury except as may be required of the University by law.

☐ I understand that in the event of physical injury resulting from this research, compensation and/or medical treatment may be available from _____ Corporation (who is sponsoring this research). I understand that if I believe that I am eligible for compensation or medical treatment, I may contact:

Name_____

Address_____

_____

Phone of sponsoring company _____

However, there is no compensation and/or payment for medical treatment from the University of Illinois at Chicago for such injury except as may be required of the university by law.

9. ADULT CONSENT (a. Will apply unless b. Is completed).

a. I acknowledge that I have been informed that this procedure is not involved in my treatment and is not intended to benefit my personal health.

b. I acknowledge that I have been informed that this procedure is also designed to assist in maintaining or improving my personal health and will benefit me personally in the following way:

_____

I acknowledge that _____ (investigator) has explained to me the risks involved and the need for the research; has informed me that I may withdraw from participation at any time and has offered to answer any inquiries that I may make concerning the procedures to be followed. I freely and voluntarily consent to my participation in this project.

I UNDERSTAND THAT I MAY KEEP A COPY OF THIS CONSENT FORM FOR MY OWN INFORMATION.

x_____		_____
Employee Volunteer signature	Date	(Type Name)
x_____		_____
Investigator signature	Date	(Type Name)
x_____		_____
Witness of Explanation signature	Date	(Type Name)

Thus, in addition to the informed consent document, a list of criteria for participant termination and a checklist that serves to document the oral explanation given to a participant may be submitted to the IRB for review to help prevent potentially adverse situations. Having an on-call psychologist or a trained counselor not connected with the study and requesting funding for psychological services in grant applications may be useful. (Also see Chapter 7, ''Managing Participants and Maximizing Compliance.'')

An emerging complex issue in research ethics involves informed consent for future analyses of blood or other tissues for measurements not yet identified, which often include genes and genetic markers. Unless otherwise noted, informed consent typically must be obtained for new measurements that were not specifically identified in the original informed consent document. Informed consent for genetic studies is currently a highly sensitive area and policies and guidelines for informed consent are currently being developed. (Also see Chapter 4, ''Genetic Effects in Human Dietary Studies.'')

Informed Consent for Dependent Groups

The basic assumption for informed consent documents is that the participant is literate or is a guardian representing the participant. Participants who are vision-impaired or functionally illiterate can be accommodated by having a study staff member read the forms and help fill them out. The document can be translated for participants who do not read English fluently. In studies with children age 5 years or older, it is advisable to include a line for their signature as well as

EXHIBIT 5-2

Women's Lipid Study: Interviewer Checklist

Name of Participant _____

_____ 1. Explanation of study benefits and handout given.
_____ 2. Explanation of study dietary rules and handout given.
_____ 3. Explanation of study schedule and handouts given.
_____ 4. Menu copies given.
_____ 5. Explanation of procedures and handout given.
_____ 6. Weight maintenance agreement signed.
_____ 7. Orientation rules explained and food take-out policy explained.
_____ 8. Consent form given.
_____ 9. Consent form signed and returned.
_____ 10. Appointment for physical examination made.
_____ 11. Medical and family history forms completed.
_____ 12. Three-day food record forms given.
_____ 13. Criteria for termination reviewed.
_____ 14. Stress due to study participation discussed.

Comments: _____

_____

_____

Participant Signature _____

Interviewer Signature _____ Date _____

that of their guardian. (Refer also to Chapter 9, ''Children as Participants in Feeding Studies.'')

Ancillary Measurements and IRB Approval

The investigator may want to add variables or otherwise modify the protocol after IRB approval. Any new measurements—for example, extra blood draws—or any additional major requirements that impinge on participant time usually must be submitted to the IRB for approval. These approvals can be obtained in two ways. If the original informed consent document has already been signed, the new measurements or requirements must be described in an appendix (which must also be signed). Otherwise, a new (revised) informed consent document must be developed and signed. In general, changes in protocol that are not substantive are quickly approved by the IRB staff without the requirement of a meeting of the full IRB.

STUDY RECRUITMENT AND SCREENING

Advertising the Study

It might be assumed that few ethical issues arise once a research study has obtained IRB approval. However, new issues can arise from recruitment and screening activities. Consider a protocol to study individuals with high serum cholesterol or high blood pressure. One approach to recruiting is to advertise free cholesterol or blood pressure testing with no further information and then invite those who meet the study criteria to participate in the research study.

This approach, however, may present ethical concerns. Presumably those responding to the free tests were concerned about their cholesterol or blood pressure and had no knowledge about being considered for participation in a research study. To be suddenly confronted with the request places them in the situation of responding without due consideration at a time when they are vulnerable. By straightforwardly advertising the study and the type of participants needed for the study, the investigators not only receive responses from those genuinely interested in research participation but also save effort in scheduling and screening many individuals who would not be interested in study participation. In addition, the investigator can obtain advice on ethical considerations raised by the content of the study advertisements and recruitment brochures by submitting them to the IRB for review. (Also refer to Chapter 6, ''Recruiting and Screening of Study Participants.'')

Explaining the Study to Prospective Participants

Because informed consent is the foundation of the ethical conduct of research involving humans, it is mandatory that participants receive a full and truthful description of all that

EXHIBIT 5-3

Women's Lipid Study Criteria for Termination of Study Participants

1. Repeated altercations with staff members, investigators, or other study participants.
2. Missing two days of meals (consecutively or not) without calling.
3. Not reporting weight honestly.
4. Not reporting unfinished food or nonstudy food consumed.
5. Unauthorized entrance into participant or staff files or staff offices.
6. Not reporting for small or big blood draws or postprandial lipid response study and not informing the staff in advance if there is a schedule conflict.
7. Violent behavior or abusive language.
8. Calling or visiting staff at home. (Investigators' home phone numbers are available to participants for use in emergencies.)
9. Harassment or threatening the safety of staff members, investigators or participants.
10. Refusing to eat study food.
11. Inability or unwillingness to provide samples according to study protocol.
12. Nonadherence to study protocol.

The investigators reserve the right to terminate study participation of any participant at any time for any reason for the benefit of the research study being conducted.

the study entails. A common issue is whether the purpose of the study should be disclosed to the participant, because knowing the purpose may influence the outcome of the study. Many IRB committees require a general statement of study purpose in the informed consent document. Disclosing the general purpose of the study and its possible importance to society is an important ethical issue and can also encourage adherence when the burden of a long study is particularly heavy. Participants have often referred to this importance as a reason for continuing in a study despite its restrictiveness. The specific measurements and what they mean need not be discussed in detail during the study if participant knowledge would bias the results of the study.

The study staff is responsible for explaining the study requirements, informing the participants of what they will be expected to do, and helping participants understand the ramifications of the requirements. For example, the requirement of eating all meals at the study site except for allowed take-out meals means that participants may experience: (1) loss of time and money required for traveling back and forth from the study site; (2) reduced family and social contact because mealtime is an important socialization time for family and friends; (3) for students, difficulty in getting their dormitory meal contract waived for the period of the study; and (4) interference with class field trips, vacations, scientific meetings, home emergencies, and leisure activities.

Potential participants are unlikely to have thought through all these consequences. They need to be raised with each candidate. A full discussion at the outset can help reduce early study dropouts because we have found that the conflict of study requirements with lifestyle is a major cause of dropouts.

When investigators are working with children, it is important to find inventive ways to describe what will be expected of them. One way to evaluate their understanding is to ask them to explain what they will be doing in the study. (Refer to Chapter 9, ''Children as Participants in Feeding Studies.'')

Screening

Screening is usually focused on obtaining study participants who qualify according to the eligibility criteria, which are inclusions and exclusions set by the study protocol. These guidelines should be objectively and rigidly followed in order to define the study population sample, the characteristics of which are guided by the research question. (Chapter 6, ''Recruitment and Screening of Study Participants,'' explores recruitment in detail.)

Some eligibility criteria are related to safety issues. It may be insufficient to ask a participant if she is pregnant; some facilities screen premenopausal women for pregnancy. Additional screening procedures may be necessary to ensure the safety of children, pregnant women, the older individuals, and particular groups of patients. Screening for HIV and hepatitis B infections is, in some cases, justifiable to protect the participant whose health might be further impaired by the study. However, IRBs may expressly prohibit screening for HIV and hepatitis B because the testing can be considered an invasion of the participant's privacy.

As noted previously, there are often potential participants with a few abnormal laboratory values who otherwise meet all the eligible criteria. What is the ethical and scientific approach for these variances from protocol requirements? This is where the safety monitoring committee's advice is invaluable. One common problem, for example, is posed by women with low hemoglobin levels. In some instances, safety monitoring committees have recommended remedial measures such as iron supplementation with provisional acceptance into the study if blood hemoglobin levels reach a particular value by the first day of the study. Because there

are usually a few low laboratory values caused by laboratory error, physiological fluctuations, and chance, a second blood test is advisable to substantiate the values in question.

Whether or not they qualify for the study, screenees should be notified of abnormal laboratory values and encouraged to see their physician or other health care provider. The screenees also should be told that the abnormal value is not a diagnosis but rather a possible problem.

In addition, it is important to screen potential participants for ability to participate because screenees often do not understand the ramifications of participation. It is human nature to commit to more than a person can reasonably accomplish. This requires sensitive inquiries concerning the distance a screenee must travel, means of transportation to the study site, family responsibilities, work schedules, and impending trips and vacations. Screenees can be ethically excluded from study participation because their circumstances would overly burden them.

Many IRB-approved eligibility exclusion criteria can include a phrase such as ''unlikely in the opinion of investigators to be able to complete the study,'' which is a nonspecific default explanation for such decisions. Although some participants can carry out the study requirements despite difficult circumstances, the investigators are still responsible for excluding from participation those screenees whose life circumstances are not consistent with the rigors of study participation. The investigators may be in a better position to make that decision than the screenee. Because some callers responding to advertisements for study participation may believe that they have been discriminated against and were denied what they considered a constitutional right to participate, study staff handling these inquiry calls should be warned that they may have to deal with angry individuals who do not meet eligibility criteria.

Study Management: Obligations to Participants and Staff

Study Participants

During a study, many issues may come up that require ethical decisions. When these issues are anticipated, provisions and decisions can be made in advance that are more likely to be ethical and yet consistent with the scientific progress of the study. Despite the best planning, new issues may arise, and it is important for the investigator to hold weekly staff meetings and be available to make responsible decisions on the spot. A lack of timely action can cause ethical problems in the long run.

Illnesses

Most informed consent documents clearly indicate that the study investigators and research institution are not responsible for health care costs incurred independent of the study. However, study staff are obliged to know about and investigate each illness to make sure that it is not connected with study participation, as potential participants may not be covered by health insurance. Alternative means of health care should be provided if participants without health insurance are accepted into a study. Participants who do not have a regular physician or health care provider should be provided with names of health care providers who would see them if the need arose. Because of the need to be informed of illnesses, it is a common practice in feeding studies to have participants fill out a daily form concerning health and medication that is checked by the study manager.

In some instances it is not clear whether a health change is the consequence of study participation. If a participant is constipated, it may be unclear whether the change of diet or some other health problem caused the constipation. Should the study pick up the cost of the health care provider's fees and any medication that might be prescribed? Some investigators would view this as a valid claim on the study and pay the fees; others would not.

Medications

The standard approach toward medications for feeding studies is to disallow the use of any medication during the course of the study and clearly state this as part of the study protocol. This may work relatively well for short-term studies, but studies lasting several months may encounter participants needing to take antibiotics, aspirin, antacids, or other medications. Ethically, the health of the participant takes precedence over study protocol.

One approach is to know when the participant is seeing a physician or health care provider and (with the participant's written permission) to have the provider call the investigator during the appointment to discuss the best medication—ideally, one that satisfies the needs of the participant and the science of the study. Another approach is to provide participants with a list of specific medications or groups of medication that either are allowable or that must be avoided, and the times in the study they must be avoided (eg, medication taken up to 3 weeks before the next blood draw may be permissible).

Handling Life Events

In studies lasting several months, a participant may have a death in the family or some other life event that requires out-of-state travel. The participant will be emotionally distraught and may declare that he or she ''must leave town immediately for at least a week.'' Study investigators are put in an ethical dilemma: do they try to talk the study participant out of going through guilt and obligation to the study or do they tolerate nonadherence to the protocol? If investigators have thought out possible alternatives beforehand, they are in a better position to describe a number of options and their consequences, which allows the participant to decide which is the most appropriate course of action. Investigators must know how many days a participant could leave each study (with packed food and food advice) and whether there are

certain times during the study that are less crucial. Very long periods of absence may mean study termination for that participant.

Emotional Problems and Stress

On occasion participants appear to be under great stress, usually because they have taken on too much. Although there are steps that can accommodate these participants, it may be more cost effective to arrange one or more appointments with a counselor (psychologist) not connected with the study but familiar with the study protocol. These visits are paid from study funds. Issues of whether study termination is appropriate and how to approach the stresses in the participant's life can be dealt with independently of study considerations.

When researchers work with children, close communication with parents is essential. Children generally ''act out'' their stresses rather than communicate them verbally.

Terminating Participants from the Study

The most common reason that participants may wish to drop out of a study is their inability to adhere to the study requirements. These participants typically will miss appointments and meal times or will eat nonstudy food. These participants do not necessarily request to terminate their participation. In some feeding trials, investigators do not terminate these participants in order to follow ''intention-to-treat'' data analysis guidelines established for the study. The investigators encourage the participants to continue with data collection, even if they are nonadherent to the research diet. In other studies, termination may be considered, and usually the study manager and investigators observe the problem and suggest to these participants that continuance in the study may be against their own best interests.

Laboratory Values That May Indicate Illness

Generally, biological samples are taken through the course of the study and study variables are assessed quickly enough that results become available while participants are still in the study. What is the ethical response to laboratory values that become abnormal during the course of the study? If the study is a double-blind clinical trial there is generally one investigator who prepares the data and presents them to the safety monitoring committee to assess. Generally, feeding studies are too short to produce enough data for this mechanism to be practical in informing participants of the abnormal values.

What is more likely to happen is that study staff making the assessments will note the abnormal value (eg, an extremely high blood pressure, blood glucose, or liver enzyme value) and bring this to the attention of the study investigators. The investigators are ethically obligated to investigate the accuracy of the measurement and its health implications, examine whether there is any connection to the study intervention, refer the participant to his or her health care provider, and determine whether the participant must be terminated from the study. Phone conversations with individual members of the safety monitoring committee can be helpful under such circumstances. Ideally, the study protocol will stipulate the conditions that warrant referral to a physician or other health care provider, as well as other ameliorative actions that can be taken (for example, providing iron supplements to individuals who develop low hemoglobin and hematocrit during the study) should be stated in the protocol prior to the start of the study.

The Semi-adherent Participant

The study manager should be attuned to the signs of nonadherence. There could be one or two participants who consume all their meals and adhere to other study protocol requirements but find it difficult to deny themselves nonstudy foods. Despite an atmosphere of nonjudgment and honesty, these participants may not report their nonadherence. The nonadherence may become known to the study staff, who must then confront the participant with the problem.

It is important to educate study staff on an appropriate and ethical approach. Participants can be ethically approached by describing the facts that are known and asked whether they want to continue their participation. If the participant wishes to continue in the study, the study manager or other investigator has a basis for identifying the personal impediments to adherence and working with the participant to address them. What if the participant denies consuming nonstudy food on a continuing basis? If evidence is insufficient, if the participant has worked out specific approaches to solving the problem, or if continued participation is valuable, it may be worthwhile to continue to work with the participant while observing his or her activities. Psychological counseling may also be useful.

However, if reasons for termination have been clearly stipulated at the beginning of the study, investigators are under no ethical obligation to retain the participant in the study.

Payment for Participation

The protocol requirements and the personal disruptions of daily life are so great in most controlled feeding studies that recognition of this disruption through financial remuneration is an important symbolic and ethical act. Some payment schedules reflect the amount of money that participants personally might have to expend on a daily basis for study adherence (parking fees, public transportation costs, occasional baby sitting) plus an additional amount for undergoing the rigors of the study. This per diem rate can be used to calculate the overall participant payment. The free food offered by the study also has a monetary value.

Even if the limits of funding were not a consideration, however, it is unwise to set payments at the level that would substitute for employment. Study participation can be motivated by the financial reward, among other things. Larger financial awards may attract participants that are in greater need of that money, which means that they are less free to

leave the study, and investigators are placed in a more difficult position in terminating their participation. This creates a great pressure for participants to remain in the study and may be considered coercive. Residential vs free-living feeding studies in which participants are free to continue their daily pursuits and sleep at home require different approaches to the timing of payments and the amount paid.

IRBs may specify rules for participant payments. Some IRBs prohibit withholding all payment until study completion; others may dislike large final (balloon) payments at a study's completion because they feel such payments constitute possible coercion of the participant to remain in the study. Others require prorated payments, especially if the amount of remuneration is large. Many investigators pay participants as the study progresses, with a small balloon payment at the end as an incentive to complete the study. Payments also can be linked to the collection of biological samples. For example, payment can be scheduled to follow a monthly blood draw. A small bonus can be an appropriate incentive for not taking out more than a set number of meals during the entire study.

All of these financial incentives are considered ethical as long as they are clearly spelled out at the beginning of the study, well-documented, and consistently applied. Policies concerning payment must be made clear to the participants from the beginning.

Another ethical concern is the promptness of the receipt of the payments. Some institutions have bureaucracies that make it extremely difficult to pay participants promptly. It is advisable to work with the institution's payment personnel well in advance of the study to expedite payment to participants.

When investigators are working with children, appropriate toys and savings bonds are a good incentive and ensure that the reward truly belongs to the child rather than their guardian.

Ensuring Meals Are Wholesome

Investigators are ethically responsible for providing participants nutritious, wholesome food. Local health departments have food safety guidelines, which should be followed rigorously even by a feeding facility not subject to official inspections. Quality assurance procedures should be in place to guarantee that food is stored, cooked, and held at the proper temperature, that dishes and utensils are properly cleaned, and that pests are adequately controlled. If gastrointestinal symptoms arise in several participants, it is the responsibility of the investigators to ascertain whether the food supplied may be the source of the trouble.

Additional Procedures and Measurements

In the course of the study, opportunities present possibilities for additional procedures or measurements. The participants' involvement should be on a voluntary basis, without compromising ongoing activities, and only after IRB approval for the addition.

Privacy and Confidentiality of Participant Materials

Investigators should plan for allowing privacy for participants when required, for example, during physical examinations or personal questions. In addition, because a great deal of cooperation among participants and staff is required in these studies, diet staff and participants cannot help but know the participants' names and identification numbers. Although anonymity is out of the question, confidentiality can be preserved.

All materials should be stored by identification number, not by name, and files should be kept locked because there are a great number of people coming and going during the course of the study day. Staff access to participant information should be limited, with someone in authority granting that access. Likewise, computer access to data files should be limited to authorized staff. Use of passwords facilitates this process. Jokes about individual participant measurements should be avoided by staff and discouraged for participants. Staff and participants should be reminded to avoid speaking about individual participants to friends and colleagues during or after the study.

Study Staff

Feeding studies place inordinate demands on research unit personnel. The principal investigator has a dual obligation to the staff: first, to ensure that they conduct themselves in an ethical and professional manner; and second, to be responsible for their well-being during the study.

Ethical Scientific Conduct and Conflict of Interest

Study investigators and staff must follow ethical conduct guidelines when interacting with prospective participants during screening, and then must continue to do so throughout the study. All eligibility criteria and procedures for randomization (if the study is a randomized trial) must be meticulously observed by staff. If recruitment is slower than anticipated, there may be a temptation to enroll participants who may not quite meet all the eligibility criteria. However, staff should execute all of the recruitment and measurement procedures exactly according to the protocol.

Study data must be recorded according to specific established procedures. If any recorded data must be changed, the documentation for these changes should indicate the date, the reason, and the names of all responsible staff members. If problems with the protocol make it difficult to carry out recruitment or implementation of other study procedures, the problems must be brought to the attention of the principal investigator. The study leadership is also responsible for making any necessary changes to the protocol—including changes to eligibility criteria. Depending on the scope of the changes, appropriate bodies, such as the IRB, safety monitoring committee, or data and safety monitoring board, may

need to be informed of these changes. Finally, principal investigators need to be cognizant of conflict of interest or the appearance of conflict of interest. Conflict of interest may arise if the principal investigator has financial ties to commercial entities that are likely to be affected by the outcome of the study. Not all conflicts have a financial basis, however. For example, researchers may have an emotional investment in the results of the study, such that they would prefer certain outcomes to others; this could influence the conduct of the protocol or bias the interpretation of results.

Requests to Participate

Faculty and graduate students are commonly accepted as participants as long as they are independent of the activities of the study (eg, they not working on a thesis that depends on the outcome of the study). However, staff of the research unit are not truly free to refuse to participate; therefore, requests for their participation are unethical under any circumstance. In addition, staff participation could lead to unintentional situations that may raise questions concerning the validity and integrity of the study, such as breaking the blind or finding out the results of primary outcome measurements before the study is over. It is therefore best not to allow staff to participate in a study, even if they request to volunteer.

Long Work Hours

Studies may be underfunded, resulting in inadequate staffing for the amount of work to be done. Study managers and graduate students are likely to bear the brunt of this situation. Investigators are responsible for ensuring that staff are not overwhelmed. Staff should be told what to expect and that they are responsible for their own well-being. This means that they must take care of themselves and communicate their needs for extra help or time.

Because of their dedication, staff members may work too long and see no other immediate solution, whereas study directors generally have a broader picture and access to other resources. This means that at least one investigator should be in frequent contact with staff so that communication is an active and ongoing process.

Handling Biohazardous Materials

Feeding studies may require collection of blood, urine, feces, or other tissues from study participants. Staff who handle these materials should be trained to know and actively carry out procedures for protection from HIV, hepatitis, and other infections. Gloves, masks, glasses, and lab coats should be worn when appropriate, and investigators should make sure these procedures are carried out.

Many institutions mandate regular blood testing for HIV and hepatitis, and also immunize staff and graduate students working with biohazardous materials against hepatitis B. Academic departments generally pay the costs. Surveillance and protection are advisable whether mandated or not.

Hiring and Firing

Each institution has rules for personnel of various classes, and the rules need to be understood and followed. Kitchen staff pose the greatest problem because some may be part-time employees and a study of any size needs sufficient staff time to cover sickness, vacations, and other times off. Student labor can also be problematic, particularly during times of exams and vacations. Many facilities successfully employ part-time personnel from the surrounding community. Occasionally a staff worker must be terminated for sound reasons such as theft. Termination is ethically easier with clear, written guidelines of what behavior is expected and what constitutes a firing offense. (Also see Chapter 20, ''Staffing Needs for Research Diet Studies.'')

Study Termination

Premature Termination

The issue of stopping a feeding study midcourse does not usually come up because such studies are usually relatively short-term. Long-term clinical trials, especially drug trials, are ethically required to consider circumstances under which a study should be called to a halt. This charge is given to an external data and safety monitoring board. The main reasons for terminating a trial prematurely are: (1) unexpected adverse side effects; or (2) the efficacy of the treatment being tested has been proven so that it is no longer ethical to deny the experimental treatment to participants in the control group. The reasons to terminate a relatively short-term feeding study are less clear-cut, but the possibilities should be thought out ahead of time and these consequences delineated. Examples might include: severe gastrointestinal effects caused by the inclusion of large amounts of a particular dietary fiber in the feeding trial; a rise in fasting blood sugar in diabetic participants; a dramatic rise in prostaglandin levels caused by a digestive irritant; or the development of skin rashes in a significant proportion of participants.

What kind of change would be grounds for stopping the study early? What proportion of participants would have to exhibit the symptom? If these issues are thought out ahead of time, the most ethical decision is easier to make.

When a study is prematurely terminated, the investigators are responsible for returning participants to their original health status. Often simply terminating the study is adequate, but participants' health should be followed to make sure symptoms have disappeared.

Planned Study Termination

Exit interviews are commonly conducted with the participants after they have completed the study. The goal of the interview is to assess adherence to the protocol and to ensure that participants leave the study satisfied that their rights have been respected. Individuals may be given their study

data at that time because one of the primary motivations for study participation is increased knowledge about oneself. It is advisable to remain available to participants after the study is terminated and respond to their calls and requests promptly.

One of the ethical problems that investigators frequently encounter is that of fulfilling promises; any promises made to participants before or during the study must be kept when the project is terminated. This is often more difficult than expected because resources are generally exhausted and there are no funds to keep sufficient staff employed. Therefore, it is important to limit promises to those that can definitely be fulfilled. These might include providing weight loss and other diet counseling, the overall results of the study, and other generally available information.

Reporting Study Results

Confidentiality for study participants must be maintained. When researchers give presentations about the study, it is tempting to use photographs of study participants engaged in the activities of protocol. These cannot be used without a signed release from the study participants pictured. Also, only identification numbers are attached to samples and data. Feeding studies often attract post hoc investigations by investigators and graduate students not originally engaged in the study. These subsequent investigators may be less sensitive to the issue of confidentiality and must be reminded of ethical behavior with respect to confidentiality. Of course, any presentation or scientific paper should present group data and disguise even the original identification number if an individual participant is singled out for discussion.

Because many people contribute to the conduct of a feeding study, the issue of who should be listed as authors on scientific papers and presentations can become a source of contention. It is best to work out these issues before the study begins. There appears to be little agreement about the inclusion of study staff as authors. A major ethical concern is the tendency of investigators to *include* as authors technicians who have performed some of the biochemical analyses but *exclude* dietitians who have had major responsibility for the development and delivery of the diets that form the independent variables of the study. Another tendency among investigators performing post hoc analyses is the failure to credit the investigators who have overseen the conduct of the study. It is important that the principal investigator provide strong leadership to ensure that individuals having a substantial contribution to the study are honored with authorship or at least acknowledgment for their contributions. There are suggested guidelines for assigning authorship and order of authorship (7, 8), which may help to resolve some of these emotionally charged situations.

Conclusion

Ethical considerations and the safety of participants are an overriding concern in human research studies. Principal investigators are responsible for the ethics and safety of a study, and their efforts are assisted by organizational structures. The IRB is the primary organizational structure that provides guidance to investigators and assurances to funding agencies that the research protocol is ethical and safe for participants. Safety monitoring committees and external data and safety monitoring boards also may be used to advise investigators in the planning and designing of the study and later in monitoring safety, recruitment, data quality, and overall study progress. Professional organizations also support ethical conduct through development of a code of ethics for their professions.

In planning a study, principal investigators must be aware of participant burden when developing data collection procedures, including the degree of invasiveness and the frequency of collection. After the study protocol is developed, investigators must seek IRB approval for the protocol. An accurate, instructive, well-written informed consent document is key to conducting an ethical study and receiving IRB approval.

Issues of ethics and safety arise throughout the study: during recruitment and screening, during the course of the study, and at the conclusion of the research. Advertisements for recruitment must be ethical, and comprehensive explanation of the study to potential participants is essential so that informed consent is truly informed. During screening and during the course of the study, procedures concerning notification and referral to other health care providers should be in place. These are activated if laboratory values are outside established norms or when clinical measurements exceed thresholds for which standard treatment guidelines exist. During the course of the study, principal investigators must make sure policies regarding participant illnesses, medication needs, life events, and stress are ethical. Ethically based policies must also be in place for nonadherent participants or for terminating participants from the study. Monetary incentives must not be perceived as coercive. Particularly important in feeding studies is the attention paid to quality control of the foodservice and assurance of safe and wholesome meals. Strict confidentiality and privacy must be maintained throughout the study, and conflicts of interest must be avoided. Principal investigators also bear some responsibility for the well-being of their staff.

After the conclusion of a study, whether terminated prematurely or as planned, all promises made to the participants must be kept, and study results must be reported in ways that maintain the confidentiality of the participants. Ethical issues regarding authorship of papers must also be carefully considered.

Planning, conducting, and concluding an ethical, safe study of high scientific merit with human subjects requires safeguards, assurances, and continual oversight, but also provides the ability to answer important research questions. Thus, ethically conducted human feeding studies are extremely rewarding, as the information they generate provides the scientific basis for promoting better health for individuals and the general public.

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