

Perspective: US Documentation and Regulation of Human Nutrition Randomized Controlled Trials

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ABSTRACT

Training to ensure good documentation practices and adherence to regulatory requirements in human nutrition randomized controlled trials has not been given sufficient attention. Furthermore, it is difficult to find this information conveniently organized or in a form relevant to nutrition protocols. Current gaps in training and research surveillance exist in clinical nutrition research because training modules emphasize drugs and devices, promote reliance on monitoring boards, and lack nutrition expertise on human nutrition research teams. Additionally, because eating is essential, ongoing, and highly individualized, it is difficult to distinguish risks associated with interventions from eating under free-living conditions. Controlled-feeding trials provide an option to gain more experimental control over food consumed, but at a price of less external validity, and may pose human behavior issues that are unrelated to the intervention. This paper covers many of the expected practices for documentation and regulation that may be encountered in planning and conducting nutrition intervention trials with examples and references that should be useful to clinical nutrition researchers, funders of research, and research institutions. Included are definitions and guidance on clinical nutrition research oversight (institutional review boards, data safety and monitoring boards, US FDA); participant safety; standard operating procedures; training of investigators, staff, and students; and local culture and reporting requirements relevant to diet-related clinical research conduct and documentation. *Adv Nutr* 2021;12:21–45.

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Overview: General Introduction

The importance of documentation and the need to comply with applicable regulations are too often given insufficient attention in the training of nutrition scientists, as well as in the planning and conduct of their research studies. There are some unique considerations and perspectives for diet-related nutrition intervention research that will be addressed in this paper. For all research endeavors, good documentation practices help to both ensure data and information are generated and archived accurately, and that information is transferred in a reliable, consistent manner to avoid dishonesty and fraud. It is an essential component of the rigor and reproducibility of science. Specific to nutrition trials, documentation of the source and analysis of the food stuff or bioactive ingredients is critical. The idiom “If it isn’t

documented, it didn’t happen” underscores the significance of documentation.

This paper is part of a series that covers guidelines to conduct clinical nutrition, as described in an introductory paper (1). The series includes guidelines for designing, conducting, documenting, and reporting human nutrition randomized controlled trials (RCTs) to assist anyone conducting, supporting, or regulating human nutrition research. The regulatory environment of the institution for the Human Research Protection Program was introduced in the preamble to this series (1). This paper provides details on the role of the Institutional Review Board (IRB) and training and monitoring of staff. Human nutrition RCTs often involve other institutional partners as well (see **Box 1** as an example). Some institutional governing bodies may

be invisible to the study team until a problem occurs (see section entitled “Awareness of Local Culture and Reporting Requirements”). Beyond the local work environment, a clinical nutrition research study may involve a Data Safety and Monitoring Board (DSMB). Some studies may involve oversight by the US FDA, USDA, NIH, Department of Defense, or other federal agencies depending on the nature of the intervention and whether an Investigative New Drug (IND) determination is required or samples are to be shipped internationally.

Box 1:
Institutional partners for conducting-controlled feeding studies—the example of Camp Calcium

Camp Calcium was a series of 11 controlled-feeding and metabolic balance studies in adolescents conducted at Purdue University between 1999 and 2010. Adolescents were fed a supervised, controlled diet in a venue of a summer research camp. The usual design was a crossover of two 3-wk residential periods separated by a washout period when participants returned home. Many institutional partners were involved in Camp Calcium. The studies were approved by the Purdue University and Indiana University School of Medicine IRBs. The participants were housed in university housing and participated in recreational and educational activities on and off campus in collaboration with many campus partners (housing, conferences, transportation, academic departments). They were fed controlled diets designed by research staff but with input from partners (food service, purchasing, companies donating foods and beverages). Research procedures included preparing and

administering stable calcium isotope tracers (pharmacy, hospital or clinic, Radiation Safety Officer for inspecting hoods for IV preparation). A large research staff was hired and included visiting students and faculty from national and international institutions (Business Office, Registrar, International Student Office). Camp staff were trained extensively by research staff, the Purdue University Hospital, Fire Department, Police Department, Housing, and Conferences staff. In 2000, when boys were to be enrolled for the first time, the university convened a team to develop SOPs for recruiting and managing risks that included Housing, Police, Fire, Risk Management, and the Office of International Equity. Sample storage included >30 freezers in the Department of Nutrition Science. All individual data have been made available to the public on a Purdue-developed site (2).

This paper covers aspects of documentation and regulation that might be encountered in planning and conducting clinical, diet-related research and good practices applicable to all studies, regardless of the sponsor. Developing standard operating protocols (SOPs) helps meet documentation requirements and perform high-quality research. Conducting human nutrition RCTs carries great responsibility and vulnerability to investigators, participants, and institutions. To protect all parties, there are multiple steps and governing principles that must be navigated, but when adhered to, the principles enable investigators to determine whether/how diet can influence diet–health relations.

Definitions. The US Department of Health and Human Services (HHS) passed a revised version of the Federal Policy for the Protection of Human Subjects [45 Code of Federal Regulations (CFR) 46 Subpart A] effective on 21 January 2019. This policy is referred to as the Common Rule and it was adopted by HHS and 15 federal agencies. Unfortunately, the Common Rule only applies to federally funded research and excludes the US FDA. Global harmonization, as well as with non–federally funded research, would be a next step. A model may be found in principles established for pharmaceutical research. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) brought together the regulatory authorities and pharmaceutical industry to achieve greater harmonization worldwide toward the development of safe, effective, and high-quality drugs.

Diet-related Intervention Documentation

Diet-related interventions can include diet and/or behavioral manipulation, provision of foods or entire meals, or delivery of dietary components in single food items or supplements. Discussions on selecting the interventions and controls are covered in other parts of this series (3). This section covers the documentation that should occur for addressing safety, appropriate preparation, storage, delivery, and monitoring of the interventions and data collection.

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Supplemental Boxes 1–4 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances>.

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Abbreviations used: AE, adverse event; CFR, Code of Federal Regulations; CITI, Collaborative Institutional Training Initiative; COVID-19, coronavirus disease 2019; CRC, Clinical Research Center; CRF, case report form; DSMB, Data Safety and Monitoring Board; DSMP, Data Safety Monitoring Plan; GCP, Good Clinical Practice; HHS, Department of Health and Human Services; HIPAA, Health Insurance Portability and Accountability Act; IB, Investigator’s Brochure; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IND, Investigative New Drug; IRB, Institutional Review Board; PI, principal investigator; RCR, Responsible Conduct of Research; RCT, randomized controlled trial; SAE, serious adverse event; SOP, standard operating protocol; SUSAR, suspected unexpected serious adverse reaction; UP, unanticipated problem.

The types of approaches to diet-related interventions are broad and, therefore, the appropriate documentation required takes many forms. Much depends on the level of safety concerns about the intervention and whether the intervention is in a new form or delivered in a way that is new to humans. Any study, whether on a food, food component, supplement, or other entity, that assesses the effect of that substance on the diagnosis, cure, mitigation, treatment, or prevention of disease requires an IND or an appropriate waiver from the US FDA (see **Box 2**). Given the differing types of diet-related interventions, the required documentation varies. **Table 1** provides a listing of the recommended information to be considered for different types of diet-related interventions. Overall, the goals should be to understand the safety and risk to those participating in the trial, as well as the specific needs for maintaining a consistent delivery of the intervention and data collection.

Box 2:
Diet-related interventions and IND applications

The US FDA regulates products based on the intent of use. Specifically, the FDA defines drugs as, "...articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals for a therapeutic purpose" (4).

The US FDA defines food as articles used for food or drink (i.e., primarily for taste, aroma, or nutritive value), chewing gum, and articles used as components of food, drink, or chewing gum, as long as these substances are not being used for a therapeutic purpose (4). Foods and nutrients used to prevent or treat a nutrient deficiency are exempt from the drug definition. However, the definition of a drug extends to clinical investigations, both those for commercial or noncommercial purposes, and does not consider whether the product being tested has known safety and low risk (e.g., GRAS). Although this definition has been in effect for many years, it has not been enforced for clinical investigations on foods until the issuance of 2013 guidance from the US FDA, which clarified that studies not specifically part of a drug development pathway also require an IND if the intended use of the test products meets the definition of drug (4). The issuance of this guidance prompted a strong response in the nutrition community and resulted in the US FDA issuing a stay in October 2015 for certain parts of the guidance related to conventional foods. Currently, an IND is not required for the following types of studies (5):

- Clinical studies designed to evaluate whether a conventional food or dietary supplement may reduce the risk of a disease, intended to support

a new or expanded health claim, and conducted in a population that does not include individuals <12 mo old, those with altered immune systems, or those with serious or life-threatening medical conditions.

- Clinical studies designed to evaluate a nutritional structure/function effect of a conventional food or dietary supplement. Examples of studies that would not require an IND include the effect of iron on hemoglobin concentrations (considered a nutritional effect) or on blood iron concentrations (bioequivalence/bioavailability study), isoflavone and bone metabolism (a structure and function effect), and the finding of a food component to a receptor in a target tissue (a structure and function effect).
- A clinical study to evaluate the safety or tolerability of a food or ingredient generally does not require an IND provided the target outcome is not indicative of a treatment or mitigation of a disease or condition.

Consultation with the US FDA is advised for other studies, or if an investigator or IRB is uncertain as to whether the food or ingredient requires an IND before conduct of a clinical study (6). If the research is funded by the NIH, a request must be made to the US FDA for exempt status for an IND. The US FDA has published information on how to determine if a waiver is needed and contact information for guidance (4). The US FDA may be able to provide guidance via informal communication, although will require submission of a written summary in some cases (5).

Documentation for test interventions in human nutrition RCTs generally covers safety, efficacy, and integrity (i.e., compliance, fidelity, purity, stability of compounds of interest) of the intervention. A main difference of clinical trials for diet-related foods is that the foods or their concentrates or constituents often have evidence of safe use and existing documentation on safety (e.g., Generally Recognized As Safe, New Dietary Ingredient). Therefore, safety considerations for food-based interventions involve understanding such aspects as potential allergens, food handling, and risk of microbiological contamination, which are less of a concern for extracts and studies with defined substances. However, some food components, such as those produced with a novel process or being used at high levels not covered by existing uses, require consideration of safety before use in humans, and thus the documentation for these studies may be more similar to that required for later-phase drug studies.

Some government-based guidance on documentation exists for certain types of clinical trials. For example, the NIH has published a clinical trial protocol template for phase 2 and 3 studies that are being conducted under a US FDA IND application (7) and a draft protocol template

TABLE 1 Documentation needs for different types of diet-related interventions¹

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Examples and Intent of Use	<ul style="list-style-type: none"> To support a new health claim petition of structure/function claim for a dietary substance or food For use in the diagnosis, cure, mitigation, treatment, or prevention of a disease (e.g., use as a drug) To obtain bioavailability, safety, or physiological outcome data (not indicated as a drug use) of a new dietary substance To obtain bioavailability, safety, or physiological outcome data of a currently marketed dietary substance produced by a new manufacturing process or in a new form or composition that could substantially change the structure or availability of the active food, component, or supplement 	<ul style="list-style-type: none"> To support a new health claim petition or structure/function claim for a dietary substance or food To obtain bioavailability, safety, or physiological outcome data (not indicated as a drug use) on a food or supplement currently marketed, when the use is consistent with current or allowable usage (e.g., food additive petition, GRAS, NDI, ODI) To obtain bioavailability, safety, or physiological outcome data (not indicated as a drug use) of a substance manufactured by a new process or in a new form that would not substantially change the structure or availability of the active food, component, or supplement 	<ul style="list-style-type: none"> To obtain physiological outcome data on changes in dietary patterns, such as altering the ratio of saturated-to-polyunsaturated fats, on health outcomes 	<ul style="list-style-type: none"> To understand the effect of specific dietary instructions or guidelines on nutrient intakes and associations with health outcomes To assess factors related to adherence with dietary guidelines and recommendations
Considerations	<ul style="list-style-type: none"> Some studies may require an IND (10) application or other regulatory documentation (e.g., Investigator Brochure), which would include much of the information noted in the columns below If foods are provided in bulk or as controlled diets, or are prepared on-site, some safety and quality recommendations under "Dietary/Meal Pattern Manipulations" column should be considered 	<ul style="list-style-type: none"> Some studies may require an IND (10) application or other regulatory documentation, which would include much of the information noted in the columns below If foods are provided in bulk or as controlled diets, or are prepared on-site, some safety and quality recommendations under "Dietary/Meal Pattern Manipulations" column should be considered 	<ul style="list-style-type: none"> Some studies may require an IND (10) application or other regulatory documentation, which would include much of the information noted in the columns below If foods are provided in bulk or as controlled diets, or are prepared on-site, some safety and quality recommendations under "Dietary/Meal Pattern Manipulations" column should be considered 	<p>—</p>
Description of the Intervention	<ul style="list-style-type: none"> Total amount of test substance to be delivered/consumed Route of administration Duration of intervention Chemistry/composition of the active substance, including source and important components Composition of the product containing the active substance, including excipients and amount per serving Composition of the control/placebo 	<ul style="list-style-type: none"> Total amount of test substance to be delivered/consumed Route of administration Duration of intervention For manufactured foods and supplements, the Nutrition Facts Panel or Supplement Facts Panel, respectively, along with the ingredient lists on the labels can be used for composition description The composition of the control/placebo should be detailed 	<ul style="list-style-type: none"> Total amount of nutrient or test foods/diets Total daily intake of foods, including menus per different caloric intake needs, and nutrition information of foods (for manufactured foods, the Nutrition Facts Panel and Ingredient List on the food label can be used for composition description) Duration of intervention Control/comparator foods/meals and menus for different caloric intake needs 	<ul style="list-style-type: none"> Detailed dietary instructions/counseling approach Duration of total intervention Frequency of interactions Method of delivery (e.g., group vs individual, Web-based, etc.) Control or comparison interventions or conditions

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TABLE 1 (Continued)

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Safety and Justification	<ul style="list-style-type: none"> Justification for the total amount and route of the intervention Evidence of safe consumption or safety data should be available and a review by someone appropriately trained should be conducted Test products and controls/placebos should be manufactured under appropriate cGMPs Participants should receive specific instructions on safe handling and storage Documentation of amounts dispensed, returned, destroyed, and/or consumed should be performed 	<ul style="list-style-type: none"> Justification for the total amount and route of the intervention Test product use should be consistent with current GRAS or approved food additive petition (food/dietary component), or an ODI or NDI (supplement), or have evidence from marketing experience of safe use under conditions of the study Test ingredients and controls/placebos should be manufactured under appropriate cGMPs If food is prepared and not prepackaged, key personnel preparing food should have training and certification in food handling If participants take foods home with them: <ul style="list-style-type: none"> Foods should be packed in containers that do not leak or spill Provision of a food cooler and ice packs may be required Participants should be made aware of food storage and handling requirements 	<ul style="list-style-type: none"> Justifications for amount used compared to a typical serving size and evidence of safe consumption at this level Ingredients and prepared foods should be manufactured under appropriate cGMPs Individuals preparing foods on-site should have appropriate training and certification in safe food-handling procedures Foods should be appropriately stored for food safety needs, and food prepared on-site may need to be tested for safety Daily menus should be designed by someone appropriately trained in dietary assessment (e.g., RDN) to ensure adequate calories and nutrient intakes If participants take foods home with them: <ul style="list-style-type: none"> Foods should be packed in containers that do not leak or spill Provision of a food cooler and ice packs may be required Participants should be made aware of food storage and handling requirements 	<ul style="list-style-type: none"> Justification for the mode of intervention delivery, and for the length, number, and frequency of intervention contacts Describe intended mechanistic target and clinical endpoints, and the theory upon which the intervention is based Discuss known or potential problems associated with the control group chosen in light of the specific disease, health behavior, and intervention(s) being studied Identify possible unintended consequences of behavioral intervention (e.g., eating disorder, phobias)

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TABLE 1 (Continued)

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Description of Study Intervention(s) Administration	<ul style="list-style-type: none"> • Timing per each amount to be consumed/delivered with justification (e.g., multiple or single events) • Duration and the relation to meals/snack consumption, if applicable • Conditions under which administration amount or timing may be changed (e.g., scale-up dosing) • Instructions to study participants about when or how to prepare and take the study product, with details on handling of delayed or missed study product consumption • Products should be maintained in a manner such that it would not be consumed by others, and all unused products should be returned for documentation of destruction 	<ul style="list-style-type: none"> • Timing per each amount to be consumed/delivered with justification (e.g., multiple or single events) • Duration and the relation to meals/snack consumption, if applicable • Conditions under which administration amount or timing may be changed (e.g., scale-up dosing) • Instructions to study participants about when or how to prepare and take the study product, which may be provided by the label information • If a caloric food is introduced, and body weight maintenance necessary, participants should be counseled on appropriate food substitutions by someone trained and experienced in dietary assessments (e.g., RDN). • Participants should be instructed that no other individuals should consume the test products • Documentation of consumption events and lost or destroyed product should occur 	<ul style="list-style-type: none"> • For controlled meals or foods consumed only at the test site, documentation of the timing of delivery, what foods were provided to the participants, and what foods were or were not consumed should be documented; in addition, identification of who prepares and delivers the foods, and whether a quality-control check (e.g., second person reviews and signs off) has been conducted • Foods provided as pack-outs, instructions to study participants about when or how to prepare and take the study product, which may be provided by the label information • Details on handling of delayed or missed meals 	<ul style="list-style-type: none"> • Total number of full sessions and partial sessions/check-in sessions • Frequency or schedule of sessions • Details on interventionists and setting (e.g., group setting, virtual delivery, face-to-face individual sessions) • Other parameters relevant to delivery (e.g., intensity, difficulty level, intervals between tests in computer-administered applications, etc.) • Interaction participants may have with other participants

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	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Preparation, Packaging, Labeling, and Blinding of the Intervention	<ul style="list-style-type: none"> Name and address of manufacturing facility Controls under which products are produced (e.g., cGMP), and products should be accompanied with a Certificate of Analysis Any preparation by study staff and/or study participants should be described, including thawing, diluting, mixing, and reconstitution/preparation Batch-to-batch variability should be addressed Describe appearance of product and packaging Label information should include the expiration date and a generic list of ingredients or, for blinded products, possible ingredients, and coded to clearly identify the product while maintaining blinding Labels should indicate the product is for research purposes only and not to be consumed by anyone other than the participant Description of blinding of the intervention (if applicable), who is blinded/unblinded, and efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible Description of the procedures for unblinding (e.g., SAE), and measures to prevent unblinding (e.g., laboratory measurements), as well as process for reporting of inadvertent unblinding 	<ul style="list-style-type: none"> Name and address of manufacturing facility, and controls under which products are produced (e.g., cGMP), and products should be accompanied with a Certificate of Analysis, unless marketed and labeled foods/supplements are used Any preparation by study staff and/or study participants should be described, including thawing, diluting, mixing, and reconstitution/preparation Appearance of product and packaging Label information should include the expiration date and a generic list of ingredients or, for blinded products, possible ingredients and coded to clearly identify the product while maintaining blinding Labels should indicate the product is for research purposes only and not to be consumed by anyone other than the participant Description of blinding, if applicable, and efforts to ensure that the study intervention and control/placebo are as indistinguishable as possible for double-blinded studies If blinding is not an option (e.g., different food comparisons), then indicate who will be blinded (e.g., lab personnel, statisticians, etc.) or unblinded, and how the blinding will be maintained and assessed If prepackaged products are used, indicate how the product will be relabeled for blinding Description of the procedures for unblinding (e.g., SAE), and measures to prevent unblinding (e.g., laboratory measurements), as well as process for reporting of inadvertent unblinding 	<ul style="list-style-type: none"> Adequately describe all food items, and identify food brands, including description of the food items, size, and type of packaging Indicate the shelf life for each food item A protocol with standardized recipes (e.g., cooking technique, time, temperature, and specific ingredients brands/suppliers) should be developed for foods prepared in a metabolic kitchen to ensure consistency of nutrient composition throughout the trial Weight food items using electronic analytical balances that are accurate to at least 0.1 g; accuracy of the balances should be checked weekly A production sheet/log for each meal preparation should be maintained and double-signed for confirmation of food composition All prepared food items should be clearly and adequately labeled for storage The label on foods served to the participant should show a generic description and a code to preserve the masking of foods in a blinded study To ensure the test and control foods are safe for consumption, microbiological tests (e.g., <i>Salmonella</i>, pathogens, mycotoxins) may be warranted for some food ingredients or test items If participants are allowed to select items on their own, then an approach to analysis of these items (e.g., return of all food labels, providing duplicate foods, food diaries, etc.) should be considered 	<ul style="list-style-type: none"> Training of interventionists, if required, should indicate date and type of training Describe blinding of the intervention (if applicable) and methods to ensure control/placebo are as indistinguishable as possible Identify who is blinded/unblinded, methods to ensure the blinding, and procedures for unblinding (e.g., SAE); if study is unblinded, provide rationale If blinding is known to be imperfect, describe plans to assess the magnitude of the problem or manage it Provide implementation details for procedures to minimize bias, as long as this does not compromise the randomization or blinding

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TABLE 1 (Continued)

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Storage, Stability, and Variability of Study Products	<ul style="list-style-type: none"> • Appropriate storage for control and test products that takes into account consistent quality (e.g., texture, flavor and acceptability) and stability (e.g., protection from light, temperature, humidity) should be known and described • Study products should be shelf-stable for the length of the intervention, and it should be known whether the bioactive in the test food is still viable during the intervention (e.g., length, freeze-thaw cycles, etc.) • Samples of the control and intervention foods should be archived until the last participants have completed and the first analysis has been conducted in case questions on product safety or integrity arise 	<ul style="list-style-type: none"> • Appropriate storage for control and test products that takes into account consistent quality (e.g., texture, flavor and acceptability) and stability (e.g., protection from light, temperature, humidity) should be known and described • Study products should be shelf-stable for the length of the intervention and it should be known whether the bioactive in the test food is still viable during the intervention (e.g., length, freeze-thaw cycles, etc.) • Samples of the control and intervention foods should be archived until the last participants have completed and the first analysis has been conducted in case questions on product safety or integrity arise 	<ul style="list-style-type: none"> • Proper food-handling and food storage practices must be followed to prevent cross-contamination with foodborne pathogens or allergens • Appropriate storage for both control and test products to ensure food safety, quality (e.g., texture, flavor and acceptability), and stability of the intervention (e.g., viscosity, bioactives, etc.) should be known and may differ for the different foods • Study products should be shelf-stable for the length of the intervention • For prepackaged foods/supplements, storage information provided by product labels should be followed and is usually adequate • Archiving until the study is complete may be considered for some key foods, but may not be feasible for all food items 	<ul style="list-style-type: none"> • Not relevant

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TABLE 1 (Continued)

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Dispensing, Accountability, and Adherence to Diet-related Intervention	<ul style="list-style-type: none"> Unmarketed study products must be maintained in a locked controlled storage and a full inventory must be maintained at all times The approach to how study products will be obtained and/or provided to the study site should be detailed How/by whom the study interventions will be distributed at the site should be detailed Unused study products must be returned and the disposal process documented All study products should be fully accounted for in product inventory logs Participants should be given clear instructions not to share any study products and to report if study products were lost or not maintained under appropriate storage conditions The approach to compliance assessment should be clear, including what documents will be required (eg, daily log, food diary) and how compliance will be calculated If other records are required for the source documentation, these should be defined 	<ul style="list-style-type: none"> Study products should be maintained in a controlled storage and an inventory of products maintained The approach to how study products will be obtained and/or provided to the site should be detailed How/by whom the study interventions will be distributed at the site should be detailed Disposal of unused study products should be detailed, including by whom, and accounted for in product inventory logs Participants should be given clear instructions not to share any study products and to report if study products were lost or not maintained under appropriate storage conditions The approach to compliance assessment should be clear, including what documents will be required (eg, daily log, food diary), and how compliance will be calculated If other records are required for the source documentation, these should be defined 	<ul style="list-style-type: none"> Proper food-handling and food storage practices must be followed to prevent cross-contamination with foodborne pathogens, as well as quality (eg, texture, flavor, and acceptability), and stability of the intervention Foods dispensed in meals should be documented per person (daily log) and any returned items noted and weighed for compliance assessment Compliance should be monitored (eg, by inspecting returned food containers for uneaten items, and weighing and reporting uneaten items in a daily food record) Participants should be given clear instructions to eat all the provided food items; not to share food items; and to report if any food items were lost due to spillage 	<ul style="list-style-type: none"> Participants' adherence (attendance at intervention visits, exposure to intervention materials) should be documented and tracked Indicate which documents will be used for adherence (eg, attendance, time in sessions, questionnaires, etc) and how adherence will be calculated Indicate the minimum completion for inclusion in analysis

(Continued)

TABLE 1 (Continued)

	Single food, food component, or supplement not currently marketed (7)	Single food, food component, or supplement currently marketed in some form (8)	Dietary meal/pattern manipulations with provision of food/meals (8, 9)	Diet pattern/behavioral manipulations by advice or guidelines only (9)
Variability of Study Products and/or Fidelity of the Intervention	<ul style="list-style-type: none"> Batch-to-batch variability should be addressed 	<ul style="list-style-type: none"> Batch-to-batch variability should be addressed 	<ul style="list-style-type: none"> For controlled feeding with multiple menu plans, best practices include obtaining analytical composition for a random number of foods/menus to confirm the consistency of the preparation <ul style="list-style-type: none"> If dietary counseling is included in the intervention, then those providing the counseling should be trained for consistent delivery, and a plan for monitoring the administration should be developed 	<ul style="list-style-type: none"> Consistent delivery of the dietary/behavioral counseling should be addressed, as relevant, to include training procedures (such as cross-training or mock sessions) and monitoring the administration <ul style="list-style-type: none"> Alternatively, if the study purpose is to address aspects of consistent delivery and/or understand variability in delivery of an intervention, then a plan for how variability will be monitored should be developed For group- or cluster-randomized trials and individually randomized group-treatment trials, describe the plan to track changes in the structure of the groups or clusters over the course of the study
Concomitant Therapy and/or Rescue Medications, and Other Concerns	<ul style="list-style-type: none"> Indicate if/how data on concomitant medications, supplements, or other therapies will be collected List allowable medications, supplements, treatments, and/or procedures that may be provided during the study Discuss any known or potential problems associated with the intervention and/or control in light of the specific outcomes being studied 	<ul style="list-style-type: none"> Indicate if/how data on concomitant medications, supplements, or other therapies will be collected List allowable medications, supplements, treatments, and/or procedures that may be provided during the study Discuss known or potential problems associated with the intervention and/or in light of the specific outcomes being studied 	<ul style="list-style-type: none"> Indicate if/how data on concomitant medications, supplements, or other therapies will be collected List allowable medications, supplements, treatments, and/or procedures that may be provided during the study Discuss known or potential problems associated with the intervention and/or control in light of the specific outcomes being studied 	<ul style="list-style-type: none"> Indicate if/how data on concomitant medications, supplements, or other therapies will be collected List allowable medications, supplements, treatments, and/or procedures that may be provided during the study Discuss known or potential problems associated with the intervention, and/or the control in light of the specific outcomes being studied

¹cGMP, current Good Manufacturing Practices; GRAS, Generally Recognized As Safe; IND, Investigational New Drug; NDI, New Dietary Ingredient; ODI, Old Dietary Ingredient; RDN, registered dietitian; SAE, serious adverse event

for behavioral clinical trials (9), which includes sections on intervention documentation and monitoring relevant to diet-related interventions targeted for health claims or diet/behavioral interventions, respectively. The US FDA Good Clinical Practice (GCP) guidance briefly addresses this concern by indicating that marketed products and those with well-known safety profiles may not need an extensive description and rationale for safety, and the basic product information brochures, package leaflets, and labeling may be sufficient (10). It should be noted that, for drug studies or those conducted under an IND and in accordance with GCP, an Investigator's Brochure (IB) is often required to accompany the protocol. The IB is a compilation of nonclinical and clinical data on a substance that is relevant to the study and includes a clear and concise summary of the safety and pharmacology of a substance. It is not clear whether this type of documentation would be required, or even appropriate, for meal-based interventions.

Health Canada has published the *Best Practices for Food-Based Clinical Trials* guidance document (8) that also contains helpful information for food- and meal-based interventions. The US FDA has not provided specific guidance for food- and meal-based interventions, although some sections of the US FDA GCP guidance may be relevant (10).

Dietary counseling is important when dietary changes are part of the intervention. A study schedule and timeline, with documentation of dietary pattern topics that will be covered, specific data collection parameters, and a description of the validated process that is needed to collect those data, should be developed for overall study quality-control management. Finally, when diet interventions are based on, or include testing of, behavioral theories, such as self-determination, social-cognitive theory, or transtheoretical and health beliefs, a fidelity measure to ensure the consistency of delivery of the intervention by the interventionists is important to include. For example, often a subset of the interventionists' sessions is taped and reviewed by an evaluator who is trained in the theoretical model used in the dietary intervention study.

Introduction to Human Nutrition RCT Oversight

In this section we will address the IRB and Data Safety Monitoring Plans (DSMPs) that may be required for a study of a diet-related intervention. Monitoring for the safety of participants in studies is the responsibility of all study staff [typically the responsibility of the principal investigator (PI) and those delegated by the PI], the IRB, and in many situations, an internal safety officer and DSMB, although the legal responsibility may rest with 1 individual. It is important to note that testing humans is a privilege, not a right. The IRB and DSMB have played a central role in many investigations of diet-related investigations, and they are important impartial bodies to assure that there is oversight of participant safety by persons who have no conflict of interest in the study.

Researchers have a wealth of ideas, many with the potential to enhance human health and well-being. Although the government, foundations, and industry may be interested

in supporting proposed research, they all require that the ethics of a study that involves human participants be reviewed and approved by an independent body prior to their releasing funds and before conducting any study visits with a participant.

What is human subject research?

A definition of human subject (participant) research according to 45 CFR 46 involves a living individual about whom an investigator obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens (11).

It is important to note that the concept of risk is not included. Risk is determined by the investigator and IRB and is used to guide necessary protections to research participants but does not determine whether an activity is human subjects research or not. Thus, even if a particular activity (e.g., completing a questionnaire) seems to present minimal risk it may still constitute human subject research and be governed by applicable policies (e.g., an expedited review).

The guidelines for research involving human participants stem from the Belmont report, which was written in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. It identified 3 fundamental ethical principles for using any human participants in research:

- Respect for persons. This entails protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent
- Beneficence. The aim here is to minimize harm to the extent possible while maximizing benefits
- Justice. The goal is to ensure the costs and benefits to potential research participants are equally distributed

Drawing on these principles and those described in the Declaration of Helsinki, all investigators should consider the following:

- Respect for the individual
- The right of individuals to self-determination
- The right of individuals to make informed decisions about participation in research

The "Common Rule" was drafted to codify the expectations for practices related to human subject research. The Common Rule has been adopted by 16 agencies and departments of the federal government.

Costs and benefits of human subject research

All research has risks. If all possible outcomes of a research activity were known, there would be no point in conducting the work. Research is conducted to test a hypothesis. The recruitment and consent processes are intended to ensure that potential research participants are in a position to make a free and informed decision about participation. It is not expected to guarantee no harm will come to participants. For

some forms of research, risks may be very high, including death. High-risk procedures may be approved if evidence is provided that such risks are minimized to the extent possible and that participants understand the nature and probability of suffering an adverse event. Benefits to research study participants may take different forms (e.g., monetary, health, knowledge). Some, but not all, research activities offer possible benefits to participants. Where no benefits are likely to accrue to the participants, this must be explicitly stated in the consent document. (The consent process is described in a separate section below.) Where benefits are possible, the nature and magnitude must also be delineated. The IRB will carefully review claims about potential benefits to determine the veracity of claims, that they are proportional to risks, and reflect the circumstances of potential participants (see **Box 3**).

Box 3:
Example of clinical study ethics decision

A dietary intervention trial is designed to determine whether the practice of eating 200-kcal portions of foods at 12 time points over a day versus 1200-kcal portions twice a day will alter energy expenditure. It is hypothesized that this may vary in different climates and populations, so a multicenter trial is proposed that will include samples from North America and sub-Saharan Africa. To compensate participants for the time they will devote to the various study-related measurements and activities, a monetary incentive will be offered. The question is, what is an appropriate amount? A likely criterion would be to assess the magnitude of the proposed payment relative to the individual's customary income to ensure it is reasonable and not excessive. By this standard, a participant in Chicago should receive a higher payment than one in Accra, Ghana. However, the burden and risk assumed by individuals in both settings are the same. This would dictate that they receive the same compensation. If the latter approach were adopted, the compensation could be coercive to the potential participants with lower incomes. Resolution of such circumstances will require thoughtful discussion with parties in all test sites and the IRB.

IRB

What is an IRB?

According to Wikipedia, "An institutional review board (IRB), also known as an independent ethics committee (IEC), ethical review board (ERB), or research ethics board (REB), is a type of committee that applies research ethics by reviewing the methods proposed for research to ensure that they are ethical." Under US FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor socio-behavioral and biomedical research involving human participants. An IRB can be local or commercial. The primary purpose of

the IRB is to protect the rights and welfare of human participants involved in research activities being conducted under its authority. The IRB will review research protocols and related materials (e.g., informed-consent documents, recruiting advertisements, and investigator brochures) to determine the following:

- The rights and welfare of the research subjects are protected adequately
- The risks to subjects are outweighed by the potential benefits of the research
- The selection of subjects is equitable
- Informed consent will be obtained

Based on US FDA regulations, an IRB has the authority to approve and to require modifications, or to disapprove the research. For further information, see reference (12).

Many IRBs are established and supported by institutions but operate independently with respect to making decisions about the ethics of a proposed study. The institution may impose additional requirements on the suitability of the proposed work (e.g., a study on drinking alcohol in dormitories may be deemed ethical but still not be allowed because of university policies on drinking in these facilities); however, a decision by the IRB cannot be reversed by an institution. Some institutions may choose not to support an IRB on their campus and, instead, have proposals generated by their faculty reviewed by a central or commercial IRB. It is efficient in multisite studies to have a lead IRB and then have the other sites defer to the central IRB. As of 25 January 2018, the NIH requires that a single IRB be used by all members of multisite trials supported by the NIH. This standard may be applied to trials supported by other funders but is not required. When >1 IRB is involved, different review schedules and practices can lengthen time for approval.

Why have an IRB?

For human research conducted under federal funding, the IRB serves the functional role of meeting federal requirements to enable institutions to be eligible to receive federal research support. Although initially driven by the federal government, most institutions have concluded that the ethics of proposed research is not determined by the funding source so they require the same review processes to be followed for all research involving human participants.

The IRB review process, however, may not appear consistent over time or across institutions. Therefore, it is important that investigators be aware of how the IRB at their institution functions. For example, protocols and study procedures may need to be adjusted when different IRBs are used, and this can delay the initiation of work. This has resulted in the IRB process being a source of frustration by researchers. However, in the grand scheme of all the steps in a research project (e.g., conceiving the research question, seeking and securing funding, pilot-testing procedures, etc.) it is typically not the rate-limiting step. It might help for the investigator to put him-/herself in the role of the study

participant when preparing IRB documents, and from this point of view, adherence to standards would be expected and appreciated.

Composition of IRBs.

To successfully execute its function, it is imperative that an IRB has an appropriate composition. The requirements for the composition of an IRB are described in 21 CFR 56.107. It is stipulated that each IRB shall have at least 5 members, with varying backgrounds, to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human participants. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice.

The IRB is required to have at least 1 member who has a primary concern in the scientific area of interest, but this is generally broadly applied. That is, an IRB with someone having a PhD in a biological discipline and/or an MD is often considered to have the appropriate composition for reviewing nutrition-related trials. However, given the complexities of nutrition research, it would be best practice to include a qualified nutrition professional. If not, the investigator may want to ensure that the IRB understands their specific research project and differences from a pharmaceutical study, or one that carries different considerations and risks. There are other requirements for the IRB membership and this information can be found at Institutional Review Boards Frequently Asked Questions: Guidance for Institutional Review Boards and Clinical Investigators (12). It is possible that an IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. We recommend that the IRB include a member or invited expert with nutritional expertise for the review of studies specific to nutrition.

Each institution has discretion in the process used to select and appoint IRB members, as well as the length of their term and possible compensation. Additionally, the administrative structure of the committee is not prescribed (e.g., chair, vice chair, secretary, etc.) and the responsibilities of each member may be determined to meet institutional obligations. Responsibilities may include the following:

- Successful completion of training requirements
- Expected attendance at convened meetings
- Review and reporting of proposals

- Participation on subcommittees to establish operational procedures and policy development
- Mentoring of faculty researchers

Recruitment and informed consent.

The number of participants to be enrolled and anticipated drop-out rate should be included in the application to the IRB. The number of participants should be well justified with power calculations. Recruitment is the first step in engagement of a human participant in a research activity. Approval of the recruitment approach and materials is required by the IRB prior to initiating this activity. IRBs will vary in their policies on this issue, but generally attempt to ensure that 1) advertisements accurately reflect the approved protocol, 2) recruitment materials and activities are not coercive, 3) the actual and complete costs and benefits to the individual are conveyed and understood, 4) potential participants have the opportunity to have all of their questions answered prior to making a participation decision, 5) individuals are free to accept or decline participation or drop out at any time without consequence, and 6) potential participants can seek independent advice and information (not from the research team) on recruitment and participation. It is essential that these steps are confirmed by the potential participant through his/her signature on an IRB-approved and dated informed-consent document (except where the IRB has determined such a form is not required). The documented consent form is essentially a contract with research participants, and as such, should be understandable to nonscientists. The targeted reading level is eighth grade, when possible. It governs the expectations and obligations of both parties and both are expected to honor their commitments and responsibilities. All parties should have fully executed copies of the consent document. No research activities are allowed to start prior to the approved consent being signed. Proper dating of the consent form is key to showing this rule was followed.

The recruitment and consent procedures should include those individuals who will be directly responsible for enrolling participants and obtaining informed consent. The consent process will inform a potential participant about the study and that the participation is voluntary. All known risks and anticipated drop-out rate should be described orally during the consent process and enumerated in the informed-consent form:

- Provide prospective participants information that a reasonable person would want to have in order to make an informed decision
- Present information in a way that facilitates an understanding of why one might, or might not, want to participate
- The text of the document should be worded in a way that makes complicated information easy to understand
- Include key information such as the study's purpose, risks, benefits, and alternatives

- Include a statement describing the costs that will be covered by research versus usual care
- Contain a statement about whether participants' information or biospecimens might (or will not) be stripped of identifiers and used for future research
- Have information about possible commercial profit
- State whether clinically relevant research results will be returned to the participants
- Describe whether research activities will or might include whole-genome sequencing

If the researcher anticipates sharing phenotype or genomic data with others to be part of a larger dataset or pooled analysis, they should consider looking at the NIH website that addresses this issue (13). Some language that can be added to a consent form might be the following (institutions may have developed specific language):

“Medical information (including genetic information) will be collected in this study. Genetic information (also known as genotype data) and other data about your health (also known as phenotype data) may be shared broadly in a coded de-identified form for future genetic research or analysis. We may give certain medical information about you (for example, diagnosis, food intake, age) to other scientists or companies not at this university, including to a (public or controlled access) government health research database, but we will not give them your name, address, phone number, or any other identifiable information.”

Consent is a process.

Informed consent is a process, not a document. As knowledge evolves and risks and benefits change over time, the research participant must be continually informed and offered the opportunity to decline further participation without consequence or to sign an updated consent. Should a study participant choose to withdraw from a study, for whatever reason, they must be free to do so without explanation or consequence. If they do choose to withdraw or if they are withdrawn based on defined guidelines (e.g., noncompliance, health risk), they should be entitled to some form of compensation for the time and effort they committed. Often, if there is a monetary incentive to participate, a pro-rated payment would be appropriate, and in fact, is required at some institutions. The details of the compensation must be included in the consent form approved by the IRB. Where a monetary form of compensation is not available or appropriate, other services may be offered (e.g., continued measurements or counseling).

Data security as part of informed consent.

The consent form should include information about how data will be stored and disseminated. With respect to storage, the issues are security and longevity. Who will legitimately have access to the data and what protections are in place to ensure only authorized individuals will be able to gain access. Federal regulations require that research be retained for at least 3 y after termination of the trial. However, other entities may have longer requirements. For example,

based on Health Insurance Portability and Accountability Act (HIPAA) regulations, records that contain personally identifiable health information must be retained for 6 y from the date of signed consent. Other entities have different expectations. Investigators must determine which rules govern the records for their work. Existing guidelines indicate the minimal amount of time a record must be retained, but not the maximum. It may be that the researcher wants to store the data for a protracted time. For example, investigators may wish to keep biological samples for future analyses. The IRB or other relevant body may have language for informed consent in these cases. It is not uncommon to indicate that a biological sample (i.e., blood, urine) will be collected and archived for future nongenetic analysis. In some cases, the IRB may require more detail on how the data or samples may be used in the future. The unauthorized use of data or samples without consent constitutes a violation. This rule is intended to ensure study participants are fully informed about their commitment. IRB-approved language must appear in the consent form to indicate data and/or samples may be used for unspecified future purposes. It is then the potential participant's decision whether to consent or not.

The consent document should also stipulate how data will be shared. There are multiple facets to this process. One level is who on or affiliated with the research team may have access to what data. Second, the funding, regulatory, and institutional offices with oversight responsibility may reserve the right to inspect the data. Third, a decision must be made about whether and what data may be shared with participants themselves. Fourth, consideration should be given to future sharing of deidentified data. Finally, and perhaps the most difficult issue, is how planned and unplanned findings may be distributed. How will a situation where an observation that is unrelated to the study, but of potential health importance to the participant, be handled (see **Box 4**).

Box 4: Example of unexpected findings about the health of a participant

A clinical trial is conducted to explore how the ingestion of sweet and bitter foods differentially activate brain reward systems. The protocol calls for neural imaging by fMRI after oral exposure to foods with varying sensory properties. Participants were screened to be healthy adults. During the conduct of the trial, the technician conducting the imaging procedure notices a mass in a participant's brain. What is the responsibility of the PI to address this finding? What should they tell the participant and/or others responsible for their health? Options include:

- Nothing, the finding is not part of the trial so not of their concern
- Nothing, they may be a strong researcher, but they are not a clinician so are not qualified to make a diagnosis

- Contact a study physician to review the observation and data and make a diagnosis and inform the participant of the finding
- Inform the participant that they made an observation that they think the participant should know about, but to acknowledge they are not a clinician and cannot make a diagnosis. Rather, they recommend the participant should contact their personal health care provider and that with the participant's permission, they will release the findings they have made
- Contact the participant's health care provider directly to ensure there is appropriate follow-up.

The correct response is largely determined by the language in the consent document. If a trial is to be conducted and there is a likelihood of an ancillary, potentially negative finding (e.g., high probability of succumbing to a lethal inherited disease), it should be clear as to whether the participant wants to know of such a finding. If a finding is made, it should also be clear whom the PI is responsible to contact (e.g., participant, study physician, participant's personal physician) and what information they should share. However, under any scenario, a researcher who is not qualified to make a clinical diagnosis should refrain from doing so and should know how to convey any findings in a nonalarming way to the participant.

Deception studies. Some research involving human participants requires that the full or true purpose of the trial not be disclosed during the recruitment and consent processes or during testing because knowledge of the aim could confound the outcomes. These are termed deception studies and require extra scrutiny by the IRB because these types of studies violate the principle that participants should understand the nature of the study so they can make an informed decision about participation. If the IRB determines appropriate safeguards are in place and the benefits of the work outweigh the risks, such work may be approved. However, commonly, there is a requirement that, following completion of data collection, participants be fully informed about the work and should be offered the opportunity to approve or deny the use of their data. If they choose the latter, their data must be destroyed.

Vulnerable populations. Vulnerable populations are composed of individuals who may not be in a position to adequately evaluate the risks and benefits of their participation in a research activity; they are in a compromised position relative to making a free choice and/or are at heightened risk. The CFR identifies vulnerable groups as 1) pregnant women; 2) fetuses, neonates, children; and 3) prisoners. Under selected circumstances, however, the IRB may also consider other populations as vulnerable and in need of special protections (e.g., employees, students, individuals

with cognitive impairment, comatose individuals, people in the military, refugees, ethnic minorities). For such groups, the IRB may require that accommodations be made to ensure each individual is respected as an autonomous agent and his/her ability to volunteer is not compromised. Vulnerable populations should not be excluded from research as the findings from studies may hold different implications for these groups, and this can only be determined by direct testing.

When research involves minors, who are not considered able to adequately judge the costs and benefits of participation in a research activity so cannot legally give consent, consent must be obtained from a parent/guardian. In addition, when possible, the minor must give "assent" (agreement to participate). When a minor is 13–17 y of age and is either married or has a child, they are able to provide consent for themselves and/or his/her child, but it is best to consult with the IRB about specific cases.

If an IRB regularly reviews research that involves a vulnerable category of participants, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of ≥ 1 individuals who are knowledgeable about and experienced in working with those participants.

Protection against study risks. It is important to consider how risks to participants will be managed in the human nutrition RCT. This section in the consent form should reflect what is in the Human Subjects section of any grant application.

It is important that the study population in research will be safe when following the protocol. Inclusion criteria and exclusion criteria that are specifically related to intolerance of the diet-related intervention need to be detailed in the IRB-approved protocol. In addition, details on recruitment goals following a timeline should be provided. Assurance is needed that participants are willing to participate for the duration of the study and have no physical or psychological illness that would prohibit them from participating. Protocols may need to be revised or developed to protect the safety of volunteers and staff during situations of greater risk. See **Box 5** for an example of a protocol developed during the pandemic associated with coronavirus disease 2019 (COVID-19).

Box 5:
Example of unexpected changes to a protocol due to a pandemic

A clinical trial is conducted to explore whether vitamin D alters physical performance (Timed Up and Go) and self-reported health [Short Form-36 (SF-36)]. The major safety test is to measure serum calcium at each visit to check for hypercalcemia. Due to the COVID-19 pandemic and an inability to safely perform in-person visits, modifications of the approved safety

measure and protocol must be made. The study team determined that some aspects of the study visits could be done by phone including the SF-36 and collection of adverse events and concomitant medications. However, the subject cannot safely have a blood sample taken without risking exposure to COVID-19. It is important to notify the IRB of the proposed changes to the protocol and what other safety measures can be implemented. For example, although a serum sample cannot be taken, you could inform the study subjects to look for potential symptoms of hypercalcemia such as the following:

- Loss of appetite
- Nausea and vomiting
- Constipation and abdominal (belly) pain
- The need to drink more fluids and urinate more
- Tiredness, weakness, or muscle pain
- Confusion, disorientation, and difficulty thinking
- Headaches
- Depression

If there is any concern, the subject can be told to stop taking the supplement until a blood level can be checked. If the research clinic is open and the subject can visit during this time, besides adhering to the IRB-approved protocol, guidelines from the university/institution and state need to be followed. As appropriate, the funding agency and federal guidelines and regulations (particularly from the CDC) should also be taken into consideration.

The pandemic may result in behavioral changes. For example, public health measures may alter food intake, (e.g., access, appetite, food choice), physical activity, sleep patterns, stress, and other behavioral and physiological responses with implications for data validity. Therefore, behavior changes, particularly those that may impact study outcomes, should be assessed.

All changes to study visits should be documented and reported to the IRB as per their guidance. In this example, a protocol deviation form could be completed for each altered study visit. If the study is operating under an IND, the FDA should also be informed of any alterations in the study as a result of COVID-19. The FDA has posted guidance on how to report this information for an IND at:

<https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic>.

Details on the potential risks associated with the diet-related intervention must be included in the protocol and consent form. The Potential Risks section should include the risks for study participants from all aspects of the study, including the supplement/diet being provided and the risk of blood draws or any other tests being performed. For example,

the risks of blood sampling are local bruising and possible (although rare) infections. Any potential risks associated with the diet-related intervention being given should be detailed in the informed-consent document for the study and discussed in full with each potential participant. A plan should be in place for minimization of potential risks, first ensuring that risks will be detailed in the informed consent. Known risks should be described and procedures to protect against risks include access to a safe, hygienic environment for all medical procedures and an experienced, certified staff. In the unlikely event of a complication, the location and conditions for the provision for medical care should be specifically included in the informed consent. With regard to diet-related interventions, exclusion criteria should minimize risk. Diet may be a possible treatment for some diseases and excluding individuals with that disease may be warranted. In addition, potential benefits should be described: for example, for participants randomly assigned to a diet-related intervention, a list of possible benefits would be appropriate and it should be explicitly stated if none are expected. It should be stated that all tests performed for the protocol will be at no charge to the participants.

The protocol should be written with clear language that includes investigator responsibilities and credentials as appropriate. Any changes in the protocol, including personnel replacements, must be submitted to the IRB and other pertinent regulatory oversight committees. If not part of the protocol, changes would be logged in internal documentation.

The sources of research material to be obtained from individually identifiable human participants should be described. This may include medical records, physical and biochemical measurements, or survey data. When identifiable biospecimens or private data are involved, the IRB must determine that the research could not practicably be conducted without the use of the identifiable information. If the research could be done using nonidentifiable information, then that is what should be done.

Data protection and safety should be addressed, including a safe location specifically for the research records, such as locked filing cabinets within locked offices with keys limited to research staff should be available and maintained. Ensuring that all individual identifiers will be removed from records and tests prior to data assembly and statistical analysis, and how the code numbers will be managed and substituted, needs to be specified. Last, ensure that no participant will be identified in any publication from the study. Access to the data files should be limited by both file and database password protection, ensuring confidentiality of the data.

It should be stipulated that each individual is to receive a copy of the informed-consent document. Written consent will always be obtained according to the Informed Consent form reviewed and approved by the IRBs of the relevant institution.

Waiver of informed consent.

The IRB may waive the requirement for a signed informed-consent form when the participants are members of a distinct cultural group or community in which signing forms is not the norm, and the research involves no more than minimal risk, and there is an alternative method for documenting that consent was obtained.

Post-approval monitoring.

Post-approval monitoring is a process that confirms the research study is being conducted as approved. This monitoring ensures compliance with the federal regulations and guidelines that govern research. It also helps to prepare investigators, their teams, and the institutions for external audits by granting, regulatory, and accreditation agencies. For some studies, the funder requires an independent monitor, but for any study, an independent monitor is an option. The monitor(s) will document findings, advise the PI of any deviations from the approved protocol, provide reports to the IRB, suggest improvements, and if needed, assist in implementing any required changes. The goal is to be constructive.

Monitoring is conducted on a regular basis so repeated deviations from a protocol will be reported to the IRB and other regulatory agencies so they can respond appropriately to ensure the safety and well-being of research participants. All study staff should understand their responsibility for monitoring the safety of study participants. Relevant literature should be consistently reviewed by the PI and, if there are any significant new risks, a safety-related change in the protocol, informed consent, investigator brochure if relevant (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation should be considered. For example, actions often taken in response to a significant risk finding include immediate revision of the informed-consent document, intensification of participant monitoring, revised eligibility criteria or screening procedures, enrollment freeze, consideration of discontinuation of the trial, or an audit.

A site visit may be initiated on a routine cycle by request of an investigator or due to a planned pattern or “for cause” (i.e., a deviation or problem was identified). The review may be unannounced or planned in advance by the IRB, institution, or funding agency. Therefore, ongoing vigilance is required to be prepared at any time to demonstrate adherence to all relevant policies and procedures. For planned reviews, the review team will often send a proposed agenda so the research team can be prepared with the expected data. Participant study documents, such as informed consents, surveys, debriefings, and visit notes, etc., must be maintained. The type of information typically sought includes the following:

- How many participants are currently enrolled in the study?
- Is the number enrolled in line with the number approved?
- Is a modification to add participants needed?

- CONSORT diagram
- Are key personnel performing duties as described and approved?
- Are modifications needed?
- Have there been early withdrawals from the study?
- Have they been reported to the IRB during continuing review?
- Have there been any adverse events?
- Were the adverse events reported?
- Who is responsible for conducting study procedures?
- Are procedures in accordance with what was approved by the IRB?
- Who is responsible for training study personnel?
- Are records of training maintained?
- Is there a copy of the IRB-approved protocol on file, including any continuing reviews and modifications?
- Are all personnel (i.e., PIs, co-PIs, research staff) aware of all approved modifications?
- Is a copy of the approval letter on file?
- Is the current version of the informed-consent document being used?
- Does it have the IRB stamp?
- Are waivers of documentation of consent in place for nonexempt online studies?
- Are the IRB-approved advertisements being used?
- Are study documents (i.e., applications for approval, approval letters, informed consent) maintained for 3 y?

Monitors will review the participants case report form (CRF), which is the file that is kept for each participant containing the specific participant’s study-related documents (e.g., informed consent, visit notes and debriefings, survey/questionnaires). In addition, the study monitors will also review the overall study information, often contained in a regulatory binder specific to each study, and including such documents as the IRB-approved protocol and other IRB-approved documents, the investigators’ CVs, lab certifications, contracts, etc.

DSMB

A DSMB is responsible for the oversight of the study and will oversee aspects of participant safety as well as ethics. They may also be responsible for monitoring the progress of the study in terms of recruitment. In many cases, a human nutrition RCT will require the establishment of a DSMB for oversight of the study. This may be mandated by the funding agency or by the institution. For example, NIH requires this for all studies involving human participants and has guidelines for each specific institute regarding a DSMP (14). The goal of the DSMP is to provide a general description of a plan that will be implemented for data and safety monitoring.

Typically, the PI prepares the DSMP, which contains several elements, starting with the potential risks for study participants who participate in the trial and identification of who will be responsible for oversight of the safety aspects (e.g., PI, IRB, an internal safety monitor or group of individuals, and an independent DSMB). Consideration

should be given to what data will be reviewed and how adverse effects (see discussion below) will be reported, as well as the timeline for the generation of safety reports. Blinded, controlled intervention trials require a statistician who is un-blinded to report adverse events to the DSMB. A general safety report should be sent to the DSMB at agreed-upon intervals and will include a detailed analysis of study progress, data, and safety issues (see below).

DSMB members should have no direct involvement with the study investigators or intervention. Each member should sign a conflict of interest statement that includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or noncommercial interests pertinent to study objectives.

Confidentiality of data presented to the monitoring entity will protect interim results from being revealed unless pre-approved. All data, whether in a report or discussed during a DSMB meeting, are to be confidential. Links to individual participants will be kept confidential unless safety concerns necessitate unmasking some or all data.

Safety reporting

Safety reporting is an important component of human nutrition RCTs and the IRB and DSMB often have requirements for collection of safety-related data and for reporting and oversight, should medical intervention be necessary, while maintaining integrity of the study (i.e., blinding). For example, the DSMP should contain a section on the collection and reporting of adverse events (AEs), serious adverse events (SAEs) and unanticipated problems (UPs) as well as a description of each of these, as described in **Box 6**. Typically, this report will include a CONSORT diagram and actual versus expected enrollment figures that illustrate recruitment and participation status. The study statistician should prepare data tables that summarize demographic and baseline clinical characteristics (sex, ethnicity, race, education, and age). A review of missing visits and missing CRFs will be included. Safety should also be described as aggregate tables of AEs and SAEs as well as individual listings of AEs, SAEs, deaths, UPs, and protocol deviations. Safety tables will also include any aggregate tables of clinical laboratory values. In general, the PI will be responsible for ensuring participants' safety on a daily basis and for reporting SAEs and UPs to their IRB, the safety monitor, and the DSMB. The study statistician prepares the safety reports that are required for the DSMB to review in order to ensure good clinical care and identify any emerging trends. The DSMB will monitor participant safety, evaluate the progress of the study (typically through annual or biannual progress reports that include safety concerns and adverse events), and review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Box 6: **US FDA definitions of adverse events**

The US FDA defines an AE as, "any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. An AE does not necessarily have a causal relationship with the diet related intervention or study."

An SAE is defined as an AE that results in death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, or results in a persistent or significant disability/incapacity. Any SAE should be reported to the internal safety officer and the IRB and DSMB as per their guidelines. In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when based on appropriate medical judgment they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes. The US FDA also defines several subcategories of AEs, including an adverse reaction, which is an AE that has evidence of being caused by the intervention. Adverse reactions are a subset of all suspected AEs, and are not commonly reported separately in nutrition studies, although for new ingredients or studies under IND it may be required to report them. Typically, an institution will require language that the institution is not able to offer financial compensation for injuries while participating in a study, such as "Should you be injured as a result of participating in this study, you will be responsible for the cost of this care, either personally or through your own medical insurance. You do not waive any legal rights for personal injury by signing this form."

Inherent in these definitions, and an often-required component in reporting, is the need for the investigator to evaluate the available evidence and make a judgment about the likelihood that the test intervention actually caused the AE. If categorization is required for reporting, the US FDA evidence that would suggest a causal relationship between the intervention and the AE such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with the intervention
- One or more occurrences of an event that is not commonly associated with intervention but is otherwise uncommon in the population exposed to the diet related intervention
- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur

more frequently in the intervention group than in a concurrent or historical control group

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the background literature on the intervention, which may be included in the protocol, product information (i.e., GRAS, marketing brochures), or in the case of studies conducted under an IND, in the investigator brochure. If not available in these sources, a summary of expected AEs should be developed. Some unexpected events, if serious enough, are further defined as unanticipated problems if they meet all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the participant population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

A suspected unexpected serious adverse reaction is known as a SUSAR and occurs when there are serious adverse reactions in participants given the intervention. These adverse reactions may or may not be dose related but are unexpected because they are not consistent with current information about risks associated with the diet-related intervention. Reporting an SUSAR is an important aspect of clinical trials involving any intervention, including diet-related interventions. The DSMB may create a committee to adjudicate deaths of participants.

Unanticipated problems will be reported to the IRB within 48 h. Further guidance for reporting unanticipated problem involving risks to subjects or others can be found in reference (15). US FDA safety definitions and reporting can be found in reference (16).

The definitions in Box 6 refer to the accepted and commonly used definitions in clinical trials. As discussed in the diet-related intervention section, the types of interventions are broad with a range of potential AEs, creating a range in approaches to safety. Weight-loss studies are common in nutrition studies. AEs for an obese person during weight loss include possible hair loss, dizziness, swelling of legs, and, in extreme weight loss, a possible higher risk of gallstones. All investigators should have plans for capturing and responding

to SAEs and suspected unexpected serious adverse reactions (SUSARs; defined in Box 6). Further, the US FDA has posted a draft guidance on reporting of nonserious AEs, which allows for more selective reporting when the safety profile of an intervention is well understood and documented (10). This draft guidance should be reviewed for low-risk food- and behavior-based studies that do not have safety as a main outcome. Further, in diet-related interventions, there can be a gastrointestinal response to diet changes that is minor and transient. For example, an increase in fiber can lead to flatulence, which is often minor and resolves within a week. In the current literature, some researchers call these tolerance responses and do not capture them as safety outcomes because they do not meet a definition of being a “medical occurrence.” However, other researchers categorize them as AEs, while some do not report them at all. Although not generally safety-related, tolerance reactions can affect the acceptability and overall compliance of an intervention. For diet-related interventions that have low risk for safety issues, the tolerance outcomes can be important to capture in order to translate the science into useful recommendations. Therefore, while all studies should address SAEs and SUSARs, it is recommended that studies on diet-related interventions clearly indicate how nonserious AEs and tolerance reactions were defined and documented.

Other details on safety monitoring that will take place—for example, any blood work, clinical assessments, or other tests, as well as the time frame (e.g., every visit, beginning and end only), and how the tests or assessments will be conducted (e.g., standard automated chemistry, blood pressure while sitting after a 5-min rest)—should be provided. Any preplanned algorithm for response to abnormal test or other results (e.g., reviewed by the study physician, or preplanned follow-up blood test will be done after “x” time) should also be provided. Assurance that any SAE will be followed up until it is resolved should be stated. All SAEs need to be reported to the internal safety officer, DSMB, funding agency, and each IRB following the reporting requirements per each of these agencies/groups.

The PI will be informed of SAEs as soon as they occur by the study coordinator and will notify the DSMB within 48 h of becoming aware of the event. The PI will report the SAEs and UPs to his or her IRB within 5 business days of becoming aware of the event, or according to local IRB requirements. The review of AEs, SAEs, and UPs by the IRB or DSMB may trigger an ad hoc review. For example, specific triggers for an ad hoc review or initiation of the process of an ad hoc review by the DSMB will occur if there are unforeseen deaths or the threshold for an SAE has been met. In addition, annual reports will typically be submitted to the funding agency and the IRB.

A DSMP should also describe any planned interim analyses. Interim analyses may be conducted either due to prespecified stopping rules as outlined in the protocol and at predetermined intervals or as determined necessary by the monitoring entity to assess safety concerns or study

futility based upon accumulating data. An interim analysis may be performed for safety, efficacy, and/or futility, and the reports are prepared by the unmasked study statistician or data coordinating center responsible for generating such reports. Rules for the interim analysis, and for stopping the study, based on interim analysis, should be described a priori.

SOPs

The ICH defines SOPs as, “detailed, written instructions to achieve uniformity of the performance of a specific function.” Other documentation is also used for defining how to conduct procedures of a trial, sometimes called “working practices” or simply “procedures.” SOPs are differentiated because they are specific documents that formalize the performance and go through a formal process for establishment and maintenance. In addition, when a function has an SOP for performance, any deviation from that performance is documented as well. Therefore, SOPs are often used to establish procedures for critical functions, such as conducting informed consents; transferring, handling, storing, and documenting test substances; documentation of the study conduct; managing databases and data sharing; reporting AEs; and clinical and laboratory performance for specific key outcomes. SOPs may not be needed for every function, and general clinical practice guidelines may be used for some activities. But, consideration of the SOPs that are present and/or needed to be developed should be undertaken as part of the human nutrition RCT planning to maintain transparent, high-quality studies that can be replicated.

SOPs have specific style and writing structures. An SOP for preparing SOPs is given in **Box 7**. Examples of SOPs are shown in the **Supplemental Boxes 1–4**.

Box 7: **Standard Operating Procedure to Develop SOPs**

Introduction: The page header should include the name of the organization, the department or group, and if possible, the address. The header will then include the SOP number, title, version number, page number, and effective date. Often, the author (who is typically the most experienced with the procedure in the laboratory) will be noted in the header of the SOP. A section for documenting SOP reviews with space for the reviewer’s signature and date is also included (see front page example below) and can be used for an SOP that is archived or retired/obsolete. The page footer should include the complete filename and, as appropriate, the path on the computer to find it, or Web-link. General writing guidelines for SOPs include making sure the instructions are clear, correct, concise, complete, and comprehensive and using single thoughts and short sentences wherever possible. Language should

be detailed and appropriate to the staff performing the task. Tables, matrices, bulleted lists, checklists, and diagrams can help and are encouraged when possible. The document should be written in the present tense and active voice and use gender-neutral language where possible (e.g., they/their instead of him or her). Define job titles or unusual terms the first time they appear, followed by the abbreviation in parentheses. Avoid the use of “etc.” If the list is limited, write it out in full. If a list is extensive and inappropriate to write out in full, write the term “for example (e.g.)”

NAME , e.g., Nutrition Lab, Dept or Core, etc.	STANDARD OPERATING PROCEDURE	Approval Date
Author:		SOP #: Version #:
TITLE: STANDARD OPERATING PROCEDURE TO DEVELOP SOPS		
Approvals/Revision/Dates Names/Titles of Supervisor or PI		

SCOPE/PURPOSE: This SOP describes how SOPs will be developed and managed at a research site(s). SOPs assure consistency and rigor with the design, conduct and implementation of methods in the lab and for clinical trials by providing standards and guidelines for students and staff. This is an example of how to establish procedures for SOPs and this will vary at any given institution or research program.

1. ALLOWABLE EXCEPTIONS

The SOP will be adhered unless exceptions are required. Exceptions are written as a formal note and filed.

2. RESPONSIBILITY

All persons responsible are listed, and the person who writes the SOP should be familiar with the procedure and can be the PI of the lab, the technician, or an experienced post-doc or graduate student. Development of common SOPs is critical for multisite trials.

3. PROCEDURE

I. Develop SOPs

- a. Develop a list of SOPs to meet the needs of the researchers.
- b. There should be an agreed-upon timeline allowed for the development of each SOP.
- c. If there is a PI or SOP committee, comments back to the author(s) of the SOP should be back within 5 business days.
- d. Thereafter, the authors should send the SOP back with changes to the PI or SOP committee for final approval.
- e. After approval, the SOP should be signed, and made available to others by being available in the

lab and on a website. If the SOP is not required but a guideline it could be modified by each researcher and the signature block will be left blank. This will be available as a word document.

II. Maintaining and amending SOPs

- a. If changes are implemented, the SOP will be re-issued with a new version date and similar step described above will be taken.

III. Archive SOPs

- a. SOPs will be retained for an indefinite period of time
- b. SOPs will be dated and previous versions of the SOP will be noted in the footer.
- c. SOPs will be archived electronically.

Contingencies; corrective actions: If procedures are not followed, then the supervisor should be contacted or the PI, as appropriate, for a given facility. The corrective item should be documented and there will be instruction given to the individual who did not follow procedures in the short term. If this happens again, the individual may be banned from performing the procedure or working with the instrument. This could also happen if the supervisor or PI is not satisfied with the response of the individual or their abilities. All actions will be documented.

Investigator, Staff, and Trainee Training

Proper training of investigators and staff is critical for the success of a human nutrition RCT (Figure 1). There are many training resources that are publicly available and are essential to the thorough training of clinical trial site staff. Some institutions offer clinical degrees. Certification programs are available for clinical research coordinators and associates. Required training and certifications can vary by state and institution.

The Collaborative Institutional Training Initiative (CITI) as well as NIH are excellent resources for training materials for clinical trial site staff. All NIH-funded clinical investigators as well as any site staff who are involved in the conduct of human nutrition RCTs are required to be trained in GCP (17). The NIH offers GCP training free of charge, and CITI GCP training is available to all site staff at institutions that have an organizational subscription to the CITI program. The NIH also has a policy for Responsible Conduct of Research (RCR) that requires education on the protection of human research participants for all investigators who are submitting NIH applications for grants or proposals.

Individual institutions may have additional training requirements in terms of GCP and human subject protections. The training plan for site staff participating in human nutrition RCTs should take into consideration site and IRB SOPs. Examples of SOPs that may be needed for clinical trial site staff include Clinical SOPs, Laboratory SOPs, Documentation SOPs, Data Management SOPs, Data Sharing SOPs, Material and Data Transfer Agreement SOPs, Reporting

SOPs, and Adverse Event Reporting SOPs. Examples of additional CITI trainings offered that might be relevant to clinical trial staff are as follows: biosafety, human subjects research, communicating research findings, protocol registration and results summary disclosure in ClinicalTrials.gov, and RCR.

Many IRBs may also provide training to site staff, if requested. The topics typically covered by these trainings include regulatory compliance, IRB documentation and submissions, US FDA approvals, ClinicalTrials.gov registration, and AEs (reportable new information). It is important to note that the training offerings will differ among IRBs and can be especially different between institutional (local) IRBs and central IRBs (e.g., western IRB).

HIPAA and confidentiality training is required for all site staff in a health care profession that involves access to patient medical records. In terms of human nutrition RCTs, institution-specific HIPAA language is included in the study informed consent or is provided as a stand-alone document that is signed along with the consent form. All study staff need to be trained on the national requirements as well as any site-specific requirements or SOPs pertaining to HIPAA. Some institutional IRBs provide training. If your institution does not have HIPAA-specific training for site staff, a course is available with the CITI program.

Some studies have a formal Site Initiation Visit, particularly those that are multicenter trials, and also may be required by the funding organization. The Site Initiation Visit is a training session that takes place prior to the activation of a specific clinical trial protocol. Some of the goals of the Site Initiation Visit include training the site staff on the protocol, confirming that the site is prepared to implement all required elements of the trial, and to identify any action items that need to be completed prior to the local activation of the protocol. All investigators and any site staff who will be providing significant contributions to the trial need to attend.

A successful Site Initiation Visit will contain the following training sections as well as any other additional items that are determined to be required by the site's institution, the IRB, or the study sponsor (if applicable):

- A full review of the protocol document and informed-consent form, including a detailed overview of the study timelines (study visit schedules/schedule of events), a review of key inclusion/exclusion criteria, and a review of the CONSORT diagram
- Review with the investigators on Investigator Roles and Responsibilities in terms of GCP
- Safety: definitions of AEs, SAEs, UPs, and their reporting requirements and criteria per protocol
- Discussion of the recruitment plan and objectives, if applicable
- A discussion of whether the source documents and data capture will be paper or electronic, how the data will be retained, and who will be responsible for storing

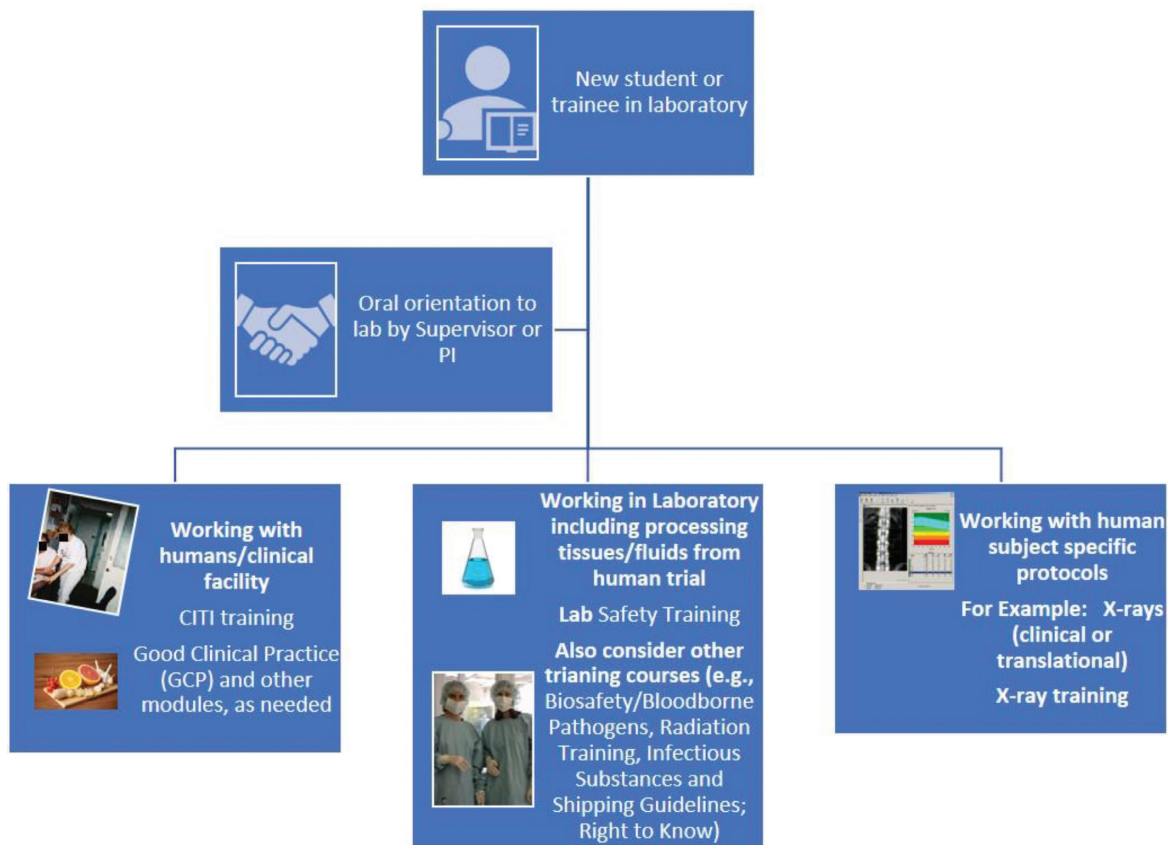


FIGURE 1 Training diagram. This schematic can provide some guidance but would need to be modified for a specific institution or trial with possible unique training requirements. CITI, Collaborative Institutional Training Initiative; PI, principal investigator.

and maintaining the data for the entirety of the record retention period. For federally funded trials, it is also important to have a plan in place regarding what data will be disseminated at the end of the study, as well as how that dissemination will occur

Protocol training for site staff should not be limited to the Site Initiation Visit. Follow-up trainings should be held when any significant amendments to the protocol/informed-consent form take place. The active monitoring by the PI or designee of staff working on protocols should be completed on a consistent basis and reviews of protocol compliance and standard practices are necessary. This proactive approach will help site staff to identify and correct any issues with protocol compliance and take action to put corrective measures in place if needed. It is essential that policies and procedures relating to the protocol are reviewed on a regular basis to ensure compliance. The PI or others may check clinical staff periodically for fidelity to study protocol by direct observation or systematic review of taped participant/interventionist sessions if relevant. New staff can be observed until they can collect data independently or a percentage of total participant interview sessions can be taped and reviewed on a regular basis. Retraining or

recertification may be necessary depending on compliance to a set protocol.

All human nutrition RCTs that are conducted in the United States are subject to inspection by stakeholders, including the funding agency or the US FDA in the case of US FDA-regulated devices or biologics. Training for potential internal, sponsor, or US FDA audits should not just occur when notice of an audit occurs. It is essential to train site staff and investigators on GCP, good documentation practices, and regulatory agency requirements prior to study start-up. It is the expectation that all study files, charts, and data should be inspection-ready at all times. The US FDA has a variety of inspection-readiness trainings and webinars on their website (FDA.gov/training-and-continuing-education) that are available to the public and would serve as a basis for US FDA- and non-US FDA-regulated studies alike.

Awareness of Local Culture and Reporting Requirements

Vulnerabilities to investigators

Most training for investigators engaged in patient-oriented research focuses on what is needed to satisfy the IRB and

DSMB. But developing good study designs and SOPs and following approved protocols are not the only considerations. Investigators also need to understand their own risks and expectations due to the legal, regulatory, and institutional environments they are in. In addition, the culture of the IRB and Human Research Protection Program varies widely across institutions and can change expectations and governance over time with change in personnel and committee members. Institutions serve the research community best if the expectations for ethical and safe conduct and reporting requirements of human research are clearly defined.

Lack of clarity by funding agencies and institution leaders or lack of awareness by investigators can have dire consequences. **Box 8** gives recent examples of risks to investigators who had approved protocols and thought they were functioning within the protocol. Investigators should be aware that they are vulnerable to personal financial, legal, and reputation costs. Institutions may only provide legal assistance to an investigator for a work-related issue once a lawsuit is filed. Therefore, incurred fees before a lawsuit is actually filed are borne by the investigators. Obviously, it is preferable to avoid a lawsuit; the President of the institution may hold the authority to decide if legal assistance will be provided to researchers supported by the institution. It is prudent for investigators to consider purchasing both professional and general liability insurance.

Box 8: Vulnerabilities to investigators

In the last 2 y, 1 Midwest IRB suspended protocols, refused to consider and approve new protocols, and required data and sample destruction by multiple investigators for the following reasons:

Safety:

- One participant consuming the diet intervention of a fruit-based drink resulted in irritation of a mouth sore
- One participant vomited after consuming a meal packaged in the CRC containing potatoes (the intervention)
- Two participants in a study in Africa on iron bioavailability receiving iron isotopes as part of a porridge reported diarrhea

Investigator responsibility:

- A graduate student collecting data in the community took consent forms home (and did not store them at work)

Participant considerations:

- Participants misbehaved

In the first 2 cases, the study was allowed to continue after assurance was provided to the IRB on

the safety of consuming a blueberry beverage and potatoes; the consent form was modified to include mouth sore irritation, vomiting, and other risks associated with eating food and drinking of beverages; and participants were re-consented. In none of the cases, did the study physician or DSMB conclude that the event was related to the intervention. Study audits were mandated. For studies sponsored by the federal government, the institution reported the suspensions to the sponsor, which triggered additional external audits. Investigators were put through remediation in some cases. Remediation workshop expenses and legal fees were substantial and were borne by the investigators. In all cases, science to be gained was lost, participant efforts were not considered, and careers were disrupted.

Assembling the research team to minimize risk

One strategy to minimize risk is to assemble a clinical research team that has appropriate training and certification or licensing for their role on the study. Working through a CRC or similar organization is ideal as the medical personnel may already be in place. Recommendations for selecting the team include the following:

- Diet interventions or diet counseling may be required or be best conducted by an RDN or someone appropriately trained in nutritional counseling
- On-site food production should be conducted by staff with training/certification for safe food handling
- Physician for diagnostic end points or medical care
- Exercise physiologist when relevant
- Dentist for dental outcomes
- Clinical psychologist for certain behavioral outcomes
- Registered nurse for certain types of medical care
- Research statistician who provides expertise needed

Payment to participants

A good accounting system is important because payments require local, state, and federal income reporting for certain levels of payments (often >\$600). In all cases, payments should be carefully tracked, which can be difficult for some situations. Different approaches to payments can be used, but all have pros and cons. Having cash on hand to pay participants may cause problems with accountability or theft, and use of checks, although helping with accountability, are time-consuming. Gift cards can be a convenient option for lower amounts of payments, but require more accountability when stipends are above the reporting requirements. One option is to use a debit card system that can protect against theft and increase accountability. However, this approach requires a W-9, and thus a social security number, and some eligible participants may not have a social security number or may be unwilling to provide their number. An institution may allow payment

through a randomly generated number or some other route.

Local reporting

Investigators need to be aware of reporting requirements beyond those of the IRB. Diet-related interventions in the form of supplements already on the market may require postmarket surveillance reporting to the US FDA. Institutions may require reporting of certain events to other relevant units, such as housing, conferences, fire department, security, etc. Participant behaviors including sexual harassment and assaults and other deviant behavior may require local reporting or notifying police and Title IX reporting.

Overall, not every possible issue that will be encountered in a study can be predicted. However, advanced planning to identify potential issues can help to develop contingency plans and to put in place extra training or more robust monitoring to mitigate risk.

Conclusions

This paper reviewed good documentation practices and multiple facets of regulatory environments with examples relevant to human nutrition RCTs. Unique to nutrition research is documenting diet interventions for the integrity and safety of the product/food/diet in procurement, preparation, storage, transport, and delivery to participants and subsequent compliance with consumption.

Some specific recommendations for nutrition interventions are discussed in this paper as follows:

- Research monitoring bodies should include expertise to evaluate diet safety and behavior of the study population as relevant to human nutrition RCTs
- Distinguishing diet-related intervention AEs from nonintervention events (participant behavior, for example) requires consideration in planning, conducting, and monitoring studies
- Training of researchers and staff needs to include diet-related SOPs

Good documentation practices are essential to the rigor and reproducibility of science but do not eliminate risk or harm to all involved. Awareness of vulnerabilities and open dialogue are critical to improving the research environment for advancing credible science. While many of these topics may be relevant to any field of clinical research, the emphasis in this paper was to highlight (with examples) specific situations encountered in human nutrition RCTs.

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