

## Review Article

# Similarities and Difference between Clinical Trials for Foods and Drugs

Frestedt JL\*

The Minnesota Diet Research Center, USA

**\*Corresponding author:** Joy L. Frestedt, Alimentix, 9445 Minnteonka Boulevard, Saint Louis Park, Minnesota 55426, USA

**Received:** May 23, 2017; **Accepted:** June 16, 2017;

**Published:** June 23, 2017

## Abstract

Many different types of clinical trials are designed by manufacturing companies and others to explore specific product features impacting human health. In addition, many government organizations regulate clinical trials and claims about trial findings globally, including the United States (US) Food and Drug Administration (FDA) and Federal Trade Commission (FTC) as well as the European Medicines Agency (EMA), European Food Safety Authority (EFSA) and other governments and agencies.

Food trials are often designed to evaluate specific marketing claims needing scientific substantiation while drug trials document the safety and efficacy of a specific drug for a specific intended use (e.g., to treat, mitigate or cure a human disease). Food trials tend to be more pragmatic and exploratory as they document human experiences with specific foods in the context of the human diet while drug trials tend to be more explanatory as they document specific drug doses and schedules and specific disease responses.

Food trials typically enroll healthy individuals while drug trials enroll patients with a specific disease type potentially needing the research treatment. Foods are complex mixtures of ingredients (e.g., plant parts, meats, eggs, chemicals, beverages, whole meals, etc.) designed to be palatable and which may have the general health effect under investigation while drugs are highly purified and designed to have a specific effect on a disease.

This narrative review will begin to differentiate clinical trials for foods versus those for drugs by briefly discussing the history of clinical trial designs, diversity in clinical trial regulations and the differences in specific food and drug trial requirements.

**Keywords:** Nutrition research; Clinical trials; Claim substantiation; FDA; EFSA

## Introduction

Health benefits of foods have been evaluated in many ways for hundreds of years and good science was at work even before the first randomized controlled clinical trial (RCT) was ever conducted. From pre-historical times when humans learned to make fire, plant seeds, harvest crops and herd animals, food has been an essential area of human research. Some believe the first clinical trial ever reported was about food. For example, in 1747, Dr. James Lind conducted a systematic clinical experiment<sup>1</sup> using citrus fruits (orange and lemon) to treat scurvy and this work was verified in 1794 when lemon juice and sugar was issued on board the *HMS Suffolk*, a British Navy ship, during a 23-week, non-stop voyage to India which landed without any serious outbreak of scurvy. Prior to this time, scurvy was a leading cause of disease and death among sailors. These types of systematic clinical experiments (i.e., clinical trials) have explored the science of nutrition and food-related health benefits for centuries.

Some believe the first RCT in medicine was published in 1948 when Dr. Austin Bradford Hill described using streptomycin to treat tuberculosis. Since then, the randomized, double-blind, placebo-controlled, tightly monitored trial has become the “gold standard” of

clinical trials for drugs in a medical setting, although many different types of clinical trials may yield valuable scientific evidence. The RCT design assigns study participants to at least two groups (treatment and control) entirely at random. Many different types of RCT are possible including (from most to least common):

1. A “parallel-group” design where participants are randomly assigned to receive either the intervention or placebo.
2. A “crossover” design where participants are randomly assigned to receive either the intervention and later the placebo or the placebo and later the intervention.
3. A “cluster” design where pre-existing groups of participants are randomly assigned to receive an intervention or placebo.
4. A “factorial” design where participants are randomly assigned to receive a particular combination of interventions or placebos.

In addition, RCTs can be designed to test for “superiority” (one is better than the other), “non-inferiority” (one is not worse than the other) or “equivalence” (one cannot be differentiated from the other) among other study designs.

The general term clinical trial, may include two basic types of studies which may be “observational” (without any planned interventional or placebo treatment; treatment is outside the control of the investigator) or “interventional” (the specific treatment is carefully planned and controlled by the investigator). Observational studies may include large-scale epidemiological studies intended to assess disease associations within populations and across lifetimes. Interventional studies include RCTs to test a particular investigational product.

Clinical trials may be pragmatic (designed to assess treatment effectiveness in routine clinical practice conditions) or explanatory (designed to evaluate efficacy of a treatment in a highly controlled setting, the archetypical drug trial). Clinical trials can use a placebo control (which compares an active product to the same product without the active component), a “historical” control (which compares previously reported data with a new group), or may have no comparator group at all (a single treatment is applied to a group without any comparator group). All of these types of trials can yield valuable scientific evidence when used appropriately to test various hypotheses or to observe various food or drug effects in humans. Appropriate study designs must consider the various types of bias when using less controlled settings and the study protocol as well as all study reports should clearly articulate these limitations and biases so the data can be clearly compared with other studies of similar food or drug effects.

Observational studies (including cohort and case cohort studies) are described as being most useful for recognizing food/drug and health associations and generating hypotheses, while experimental (interventional) studies are used to examine causation and to test hypotheses. Pragmatic clinical trials are considered low-risk because the treatments are considered standard of care in clinical practice and the results are applicable to broad a population due to the large sample size, simplistic designs and diverse settings. Each clinical trial type requires specific clinical trial methods and data analyses. For example, crossover trials inherently have a stronger statistical power because the test subject serves as their own control and thus require a smaller sample size, but completion time is often longer relative to parallel group studies because a washout period is needed between treatments and a carryover effect may be encountered which may confound the clinical trial data.

This paper describes the similarities and differences between clinical trials typically conducted for food products from those typically conducted for pharmaceutical (drug) products. The goal for this work is to clarify the state of the art for food and drug trials and to begin to explain the reasons for some of the similarities and differences between food and drug trials [1].

### Similarities between food and drug clinical trials

All clinical trials should be conducted using Good Clinical Practices (GCP) with appropriate Human Subject Protections (HSPs) and all products used in human testing should be produced under Good Manufacturing Practices (GMP) using a well-established Quality Management System (QMS). All clinical trial protocols should clearly define the study objective/s, inclusion/exclusion criteria, treatments (including stopping rules for high risk products), study measurements and statistical analyses to be used for data

analysis. The study investigator must ensure the study staff are trained and experienced, treat only appropriate study subject's and collect clinical trial data in a manner allowing appropriate evaluation of product effects on the human subject. Many authors [2-6] have reviewed good clinical trial practices which are similar between food and drug clinical trials, including the use of:

1. Safe products for human testing (food grade products food trials and drug products passing preclinical safety testing for drug products)
  - a. Production lines which do not introduce unsafe contaminants
  - b. Formulations which are well characterized considering the intended use, appropriate dose, batch variability and control products (if any)
  - c. Cellular and animal testing which may be required prior to first in man studies
  - d. Properly labeled test products (e.g., placebo should not be distinguishable from the test product, if the study is blinded)
  - e. Clearly documented shelf life stability during the timeframe of the trial
2. Appropriate trial designs, including:
  - a. Comprehensive reviews of past clinical trials
  - b. Clear study objectives and test methods
  - c. Well-defined eligibility criteria (inclusion and exclusion criteria)
  - d. Precise dosing schedules (e.g., the minimal effective dose to avoid side effects)
  - e. Effective randomization methods (if any)
  - f. Accurate/validated performance criteria (e.g., to measure clinical endpoints and to enable specific statistical plans)
  - g. Covering outcomes, compliance and adverse events
  - h. Balancing minimum sample size and time to show a health-related effect against increased costs of larger and longer trials
  - i. Enrolling study subjects representing the population of interest and allowing trial results to be generalizable to entire population of interest
  - j. Considering plateauing and sustainability of biological action (i.e., these considerations typically require longer trial periods and are generally associated with higher costs and higher drop-out rates)

**NOTE:** Optimal trial design does not always require a randomized, double-blind, placebo-controlled trial (many types of clinical trials can yield scientifically valid results)

3. Informed Consent Form
4. Trial registration (e.g., clinicaltrials.gov)
  - a. Listing prior to trial start (or within 21 days of first treatment per FDA regulations), esp. if supported by federal funding or if publication is desired.

b. Updating the listing with study results as they become available (within one year after collecting the last primary outcome data point per FDA regulations)

5. Recruitment, participant flow and data collection

6. Clinical trial oversight and compliance to ensure appropriate clinical trial staff members are trained and responsible for trial conduct including:

a. ethics/IRB (Institutional Review Board) approval and oversight

b. encouraging subject compliance with the protocol (using tangible and intangible rewards as appropriate within ethical bounds)

7. Identifying, evaluating, categorizing, reporting and following all adverse events (e.g., serious, unexpected adverse events related to the investigational products may require immediate intervention to stop an ongoing clinical trial while others will provide information on benefits or risks of the food or drug under investigation)

8. Using Good Data Practices for statistical planning, data analyses and reporting

9. Monitoring trial activities to ensure patient safety and data integrity and to ensure all adverse events are reported and followed until resolution or other protocol-driven endpoint

10. Auditing trial activities to ensure study compliance and data quality

Although the good clinical trial practices listed above may be the same for food and drug trials, many details differ between food and drug trials. Understanding these differences should contribute to the ability to design the most appropriate clinical trials for each specific food or drug product.

### Differences between food and drug clinical trials

Some of the key differences between food and drug trials are related to clinical trial objectives, trial designs, subject inclusion and exclusion criteria and overall health of the study population as well as the variability, size and cost of the clinical trial. Often the differences between food and drug trials are related to the final labeling and claims desired for the product. Any drug-related claim will classify product as a drug (even if the product is otherwise considered a food) under the US regulations and the drug claims must be substantiated with a drug trial. Food- and dietary supplement-related claims will require careful scientific substantiation and avoidance of any and all drug claims. Typically, the sample sizes and objectives of food trials are much smaller and more exploratory than the sample sizes and primary objectives of drug trials. In addition, the informed consent process is often more abbreviated in the case of a new food (or over-the-counter drug) product with limited human risks compared to a new drug (or high risk food product) with known safety concerns.

1. Food labeling and health claims must be truthful, not misleading and based on scientific evidence (often in the form of food clinical trials) while drug labeling must define why the drug should be considered safe and effective (based on drug clinical trial data). Food and drug labeling (including all claims) must meet specific legal and regulatory requirements in the country of use.

2. For US food labeling claims, food trials must test foods

under conditions which avoid allowing the US FDA to ultimately classify the food product as a drug. The goal for a food trial is often to explore a potential food effect in a group of healthy humans; however, the goal for a drug trial is often to document the specific purified/unique drug effect in a group of humans needing diagnosis, cure, mitigation, treatment or prevention of a specific disease.

3. US food labeling regulations are quite different from drug labeling requirements even though labeling is often based on clinical trial data for both foods and drugs. Foods (including whole foods, food ingredients, dietary supplements, natural products, etc.) are required to have scientific substantiation on file at the manufacturer site for any and all types of claims including (but not limited to) Nutrient Content Claims, Structure/Function Claims, Health Claims, Qualified Health Claims (QHC). In other words, food claims (including, for example, Structure/Function Claims for dietary supplements which are defined in the Dietary Supplement Health and Education Act [7]) are the responsibility of the manufacturer and must be truthful, not misleading and based on scientific evidence. Food regulations have specific, required details for food labeling (including detailed required contents in the Nutrition Facts or Supplement Facts labels/panels, etc.). Unlike food labeling regulations, the drug labeling regulations require a strict FDA review of all drug labeling including specific detailed requirements for drug "instructions for use" which provide information about how to use the drug appropriately (how much, how often, etc.) and drug "indications for use" which describe the specific disease populations and conditions of use for the drug, etc.

4. Certain food label Health Claims are reviewed by the FDA in the US and by EFSA in the European Union (EU). The clinical trial data supporting a Health Claim must be scientifically rigorous and should result in significant scientific agreement for the claim when reviewed by experts. As mentioned above, the US FDA recognizes several types of food label claims including Nutrient Content Claims, Structure/Function Claims, Health Claims, and QHC while the EU recognizes General Function Health Claims, Disease Risk Reduction Claims and Child Development or Health Claims. EFSA has a history of rejecting health claims when non-healthy subjects are used in food trials, although "at risk" subjects may be acceptable.

5. The US Federal Trade Commission (FTC) has primary jurisdiction over claims used in advertising which must be truthful and not misleading [8] and based on competent and reliable scientific evidence [9]. The meaning of the advertising claim and the relationship between the claim and the evidence must be clear and the quality and totality of the evidence must be convincing. All reasonable interpretations of each message and the totality of the messages in the claim should be substantiated. The food component subject of the claim should be the subject of the evidence which should be similar with respect to formulation, serving size and length and frequency of exposure. The study population and outcome measures as well as quality of the study design, study execution and statistical analysis should be appropriate for the study. The totality of evidence should support the claim. Favorable and unfavorable evidence should be considered.

6. As an example, the FDA drafted a guidance document to help infant formula manufacturers develop and substantiate truthful

and not misleading claims [10]. Individual structure/function statements about the infant formula ingredients must be substantiated individually and when considered together. Scientific evidence must relate to the claimed population (i.e. infant formula studies should be conducted in humans < 1 year of age), endpoints must relate to the claim (i.e. claims about brain development may use a neurological assessment as an endpoint) and the effects of the component of interest in the claim must be sufficiently isolated and appropriate (i.e., effects should differ between those infants receiving the intervention and control infant formulas). The quality of the individual studies and the totality of the evidence should be fully evaluated to determine whether the infant formula claim is supported.

7. For another example, the EU regulatory groups appear to favor meta-analyses as scientific evidence while the US FDA generally appears to prefer primary study data rather than secondary meta-analytic data. In the EU, support of food claims may use meta-analytic tools to look at effects in wide ranging studies. When considering a claim of how dairy products may improve satiety, a company may wish to rely on a meta-analysis evaluating 13 well-designed clinical trials which reported 500 mL dairy product increased satiety and decreased energy intake after consumption [11]. In this example, a claim suggesting this “dairy product may increase satiety” seems reasonable with this report on file within the company as the scientific substantiation for this food-related claim. The company would be wise to have each of the individual 13 clinical trial publications from the meta-analysis reviewed and on file as well.

8. Food trials do not typically require a safety review by the FDA before the trial can commence; however, drug trials often require an Investigational New Drug (IND) Application to be on file with the US FDA at least 30 days prior to the start of the trial. If food safety is unclear, the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) may require additional information.

9. Clinical trial data for foods are submitted to FDA for safety evaluation in New Dietary Ingredient (NDI), Food Additive Petition (FAP) and Color Additive Petition (CAP) applications and for efficacy evaluations for QHC and other types of claims based on a standard of significant scientific agreement.

10. For an NDI: “The FD&C Act contains no explicit requirement for a manufacturer or distributor to conduct human clinical studies before submitting an NDI notification. However, there may be circumstances in which you find it necessary to perform such studies because the existing history of use data, safety data, and data on population exposure do not provide a sufficient basis for you to conclude that the dietary supplement containing the NDI will reasonably be expected to be safe under its proposed conditions of use [12].”

11. For FAP and CAP applications, “Any food additive intended to have a technical effect in food and any color additive for use in foods... is deemed unsafe unless it either conforms to the terms of a regulation prescribing its use or to an exemption for investigational use. A petition for a food additive or color additive is submitted to request issuance of a regulation allowing new uses of the additive and must contain the necessary supporting data and information [13].” Applicants are encouraged to see if the substance is already listed for the proposed intended use in the Code of Federal Regulations

(CFR) including those in Title 21 of the CFR at 21CFR170-199 (food additives) or 21CFR 73-74 (color additives) or if the substance is defined in the food additive database entitled “Everything Added to Food in the United States (EAFUS) [14]. Food substances with a regulation number (e.g. 21CFR199) are only acceptable if the use and provisions for identity, specifications, and use limitations are strictly followed as defined in the regulation. Test data should be on file to verify and validate these details (Note: clinical trial data are sometimes appropriate for these food substance validation activities).

12. For a QHC: clinical studies are reviewed by the FDA and if existing data is insufficient to substantiate the substance/disease relationship, additional trials may be required by the FDA. In specific situations, the FDA exercises enforcement discretion for food-related QHC. In this setting, even though the clinical data do not meet the FDA requirements for the QHC, the FDA will allow a specifically worded QHC. The FDA maintains these details in a website entitled “Summary of Qualified Health Claims Subject to Enforcement Discretion” [15].

13. For other types of health claims (like nutrient content and structure-function claims) clinical trials are required to be on file and to substantiate the scientific content of the claim. The company must determine if the claim is adequately protected by significant scientific agreement in the published literature to be acceptable under the regulations. Understanding FDA enforcement discretion is helpful when considering each particular claim. This type of enforcement discretion is not available for drug claims in the US even though both types of claims (food and drug claims) require evidence-based review of clinical data and meta-analyses.

14. Subject selection in food trials is broad and varied, often enrolling healthy persons or those with self-described mild health conditions. These mild health conditions are typically not diagnosed or treated by a healthcare professional and healthy study subjects in food clinical trials are often not grouped into sub-populations for treatment since food is not a treatment for a condition. Subject selection in drug trials is rigorous and enrolls subjects with the particular disease type expected to respond to the specific drug treatment (based on bench and animal testing). The definition of a “mild health condition” is rather arbitrary and is not clearly defined. Certain forms of obesity and metabolic syndrome are examples. Metabolic syndrome is often defined by the patient having 3 of the following five risk factors: large waistline, high triglyceride level, low HDL cholesterol, high blood pressure, high fasting blood sugar but not including diabetes, stroke or medicated hypertension or chronic heart disease.

15. In general, more food clinical trials than drug clinical trials are conducted each year. This may be due to the lower cost, the more exploratory nature of the food clinical trials and the different regulations for food clinical trials compared to drug clinical trials.

16. Food trials are less expensive than drug trials. In the US, per subject costs for food trials are roughly \$3,000-\$5,000 (typically as part of small, less than \$500,000 marketing budget for an individual food product) while per subject costs for drug trials are roughly \$30,000-\$50,000 (typically as part of large, \$1.3B dollar R&D budget for an individual drug product).



17. Food trials were estimated to cost \$25,000-\$250,000 and one publication reported drug trials cost \$1M-50M based on data from 2004-2012 [16].

18. In the EU, food trials were estimated to cost €2,000 per subject while drug trials were estimated to cost €169,613 per subject [17].

19. Case studies and anecdotal evidence are far more common in food trials. Although these types of data are known to be less rigorous or reliable than RCT data, the findings of these bits of data can be used to develop a better plan for future food research.

20. Additional important differences between food and drug trials are related to the actual food and drug products being tested and the methods or approaches used to design appropriate clinical trials for foods and drugs specifically. For example:

21. Food products are often whole foods or complex mixtures of food ingredients being tested to support a particular claim (e.g., nutritional content, structure/function or qualified health claims in the US) while drug products are often highly concentrated and purified being tested for safety and efficacy in treating a particular disease (e.g., single molecular entity compounds designed for specific effects in the human disease).

22. Unlike drug trials, food trials need to incorporate the test food into normal dietary backgrounds and should consider annual consumption rates and individual dietary patterns as well as efficacy, safety and feasibility. An appropriate food matrix must be developed to deliver the food product and background diets as well as food dosing strategies should consider food digestion and subject factors like age, gender and health status. Unlike drug products which have entire phases of development with multiple clinical trials dedicated to determining the dose and schedule for the drug, the food dose-response relationship is typically explored using only two amounts under the same conditions in a clinical trial. For drug trials, extensive pharmacokinetic (PK) and pharmacodynamic (PD) studies are required; however, foods may not have a single molecular entity which can be marked to enable these types of trials. As a result, food trials often do not have PK or PD details available. Food clinical trials typically define exposures to the food product in Acceptable Daily Intake (ADI) or Estimated Daily Intake (EDI) amounts.

23. The stability of the functional ingredient should be considered during dispersion, food processing, storage and delivery (e.g., esterification, emulsification, suspension, and microencapsulation can be used to modify physiochemical properties of a food).

24. The minimally efficacious amount and the process of digestion as well as the product quality, taste and texture must be considered for food products.

25. Typically, food trials are designed in “free living” environments (e.g., at home, on vacation: whenever the food is consumed in the context of the background diet) while drug trials are designed in highly controlled environments (e.g., the hospital or clinic: in the context of the person’s normal medical care for their specific disease).

26. Unlike drug trials, appropriate placebo manufacturing and blinding procedures for food products may require exchanging one food-based ingredient for another and blinding may be particularly problematic for difficult to mask foods due to a unique taste or smell (e.g., cocoa, fish oil, or soy isoflavones). A few recommendations have been published to help address and manage these challenging control issues in food trials [18]

27. Choose a placebo which is well accepted by subjects and has no bioactivity

28. Prepare placebo food items to have similar appearances as well as aroma, texture and flavor profiles. The two products should be identical except for the component under investigation.

29. If the test component is a diet, provide as much of the food as possible to minimize differences in the other background nutrients.

30. Food products may be subject to specific Quality Management System standards (e.g., ISO 22000 – food safety management) and development of Hazard Analysis and Critical Control Points (HACCPs) to ensure delivery of quality food products while drug products are subject to Chemical Manufacturing Control (CMC) regulations. Both product types have the potential for independent inspections and laboratory testing reviews by the FDA.

31. Food products are highly variable and rarely have “active ingredients” separated out. Botanical drugs are a particular type of drug product which are highly variable and do not have the “active ingredients” completely separated out; however the FDA has provided guidance on the CMC documentation required for botanical products which might be useful in the food setting [19]. The Chemistry Manufacturing and Controls (CMC) defined for botanical products include the need to clearly define the botanical raw materials, the qualitative and quantitative description of the drug substance including a description of each process step in the manufacturing process along with the quality control tests performed on each batch of the drug substance (e.g., if extraction is used and the type of extraction used), the finished botanical drug product, and more.

32. Using a “totality of evidence” approach, the FDA requires all elements of processing, including raw material control and clinically relevant bioassay(s), to ensure consistent quality of the botanical drug and its therapeutic properties. Drugs often contain synthetic or highly purified active components and are more easily identified and quantifiable; while a botanical mixture is substantially more complex and much closer to a food product.

33. In addition to the difficulty in characterizing the complexity of the active components, a plant is subjected to a large number of variables from seed to harvest and manufacturing which makes the quality and consistency of the end product difficult to measure [20].

Food products tend to have less specific effects than drugs which are developed based entirely on their cellular and tissue effects prior to human clinical trial testing to generate a specific response in a diseased tissue. For example, consider Activia®, a probiotic yogurt food which has the following claim on the [www.Activia.us.com](http://www.Activia.us.com) website: “may help reduce the frequency of minor digestive issues like bloating, gas, discomfort and rumbling, when consumed twice

per day for two weeks as part of a balanced diet and healthy lifestyle” vs. Gleevec<sup>®</sup>, an oral, tyrosine kinase inhibitor designed to disrupt a specific signaling cascade in cancer cells of patients with a rare type of cancer called Chronic Myelogenous Leukemia. The health claim for Activia describes effects relevant to a healthy human and does not suggest any intended use to diagnosis, cure, mitigate, treat or prevent a specific disease. If the claim had stated “Active prevents Gastroesophageal Reflux Disease”, then the claim would have clearly classified this probiotic food product as a drug. Each word in the claim must be carefully considered to prevent classifying the food substance as a drug in the US. NOTE: QHCs are distinct types of health claims on US foods and they can be about reducing “risk of disease” in healthy humans; however no health claims can be about managing or alleviating symptoms of a disease because this type of disease claim would cause the product to be considered a drug under US regulations enforced by the FDA, FTC and others.

Foods are developed to be consumed without a medical need. In addition, effective or “functional” foods must meet personal preferences of taste, meal/snack planning and how the product fits into a person’s “nutrition” needs). Drugs, on the other hand, are developed to have a specific measured effect to meet a specific medical need (effective ingredients are isolated and concentrated based on the effect).

In general, food effect sizes are much smaller than drug effect sizes. (NOTE: smaller effect sizes would mean the trials should be larger, but funding is prohibitive if these food products are not able to be sold as drugs needed by specific persons to survive – measuring “cause and effect” for a food directly is generally not possible.)

Food trials generally have only one phase, take several weeks to months to complete, are conducted at a single study site and have minimal risk of adverse events (all foods are for oral consumption and food-related adverse events are typically related to some type of gastrointestinal disturbance associated with the digestion of the food). Drug trials have four phases (phase I: safety – may be in healthy persons, phase II: dose and schedule to treat the specific-disease types, phase III: safety and efficacy in a large representative patient population used for new drug application in the US, and phase IV: post-market), take several years to complete, are conducted at several study sites and have an expected risk of adverse events due to known drug effects on human cells and tissues (not all drugs are for oral administration and drug-related adverse events are typically related to controlling the efficacy of the drug or to some unanticipated side effect related to the drug-specific effects, metabolites or contaminants).

Foods are generally expected to be nutritious with limited side effects (often simple indigestion or gastrointestinal discomfort) while drugs are expected to have a specific, measured effect and potentially serious side effects (e.g. too much of the drug may be toxic and unsafe). Food trials are generally smaller and less controlled (because they are generally designed to explore a “food effect” on nutrition and health rather than to get a new drug approved).

Smaller clinical trials may be most appropriate for the food/nutritional industry when the food product is typically safe (low risk) and may not actually have specific effects like drug effects. The food effect may vary in different populations and smaller trials will allow individual exploration of different specific questions in each trial.

Clearly, food trials are quite different from drug trials and running food trials like drug trials will likely increase costs and timelines for trial completion and may also be expected to reduce the overall number of clinical trials completed each year. In addition, running food trials like drug trials may have a risk of generating data outside “real life” food consumption norms currently used in food clinical trials. These changes may raise questions of food data reliability for individual consumers. Mounting pressure to run food trials like drug trials may be related, at least in part, to the mature drug trial environment [21] rather than the need to have a particular type of clinical trial to measure a particular food-related health effect.

The marketing drive to provide functional health claims for foods is one drive for the increase in food clinical trials. These types of claims require scientific substantiation often in the form of clinical trial. The trial should be designed with the claim in mind. The researcher needs to identify how to accurately measure the body function in response to the food versus placebo in order to substantiate each claim about the food impacting this function.

### Best practices for food clinical trials

Effective food clinical trials are highly variable and often start with the desired claim in mind during the trial design. The food trial is built around the claim as the rationale for the study. Using thoughtful objectives and hypotheses based on a thorough review of the scientific literature, the benefits and risks of the food clinical trials are carefully considered as both safety and efficacy endpoints are defined in the study protocol. Best practices for food clinical trials include:

1. Ensuring the claim is relevant for human health and the precise meaning of the claim has been fully supported by the food clinical trial data
2. Ensuring the quantity/pattern of food consumption is possible as part of a balanced diet in the target population for the claim
3. Linking the claimed effect to the consumption of the food (e.g., strength, consistency, specificity, dose-response, biological plausibility, etc. should be fully considered)
4. Defining effects and outcomes measures clearly –although subjective measures like cognition, pain, or hunger are more difficult to measure than objective measures like hemoglobin levels or weight, food trials often use measures involving the senses: food taste, texture, and feelings of satiety, bloating, GI discomfort, etc.
5. Special considerations and measurements of specific food-related items (like the food matrix for the test material, the background diet, food-related confounding issues)
6. Considering the totality of the evidence for each specific condition of use

Compliance is monitored by careful diet analyses and sometimes includes validated biomarkers of exposure.

### Conclusion

Food and drug products and the clinical trials designed to test these products are fundamentally different. Food trials are more general and are designed to support specific health claims in healthy

(or impaired but not diseased) individuals based on the nutritional content of complex food/s, while drug trials are usually quite specific and are designed to evaluate the safety and efficacy of targeted drug treatments in patients with a specific disease based on the chemistry of a highly purified single drug. These differences in the test products (complex mixture of food ingredients in food trials and highly purified drug in drug trials) and the overall health of study subjects (healthy subjects in food trials and subjects with specific, medically treated diseases in drug trials) are distinguishing characteristics between food and drug clinical trials.

In the case of foods and food products, clinical trials are designed to examine basic health effects of complex food mixtures in healthy individuals. Drug clinical trials, on the other hand, are often multi-phase projects targeting the specific drug effects of a highly purified chemical on the human disease. The drug mechanism of action and the cause/effect relationship in a particular disease are understood in great detail and allow multiple specific, explanatory trial designs with specific measures and endpoints like objective lab values (ECG, temperature, heart rate, X-ray, hemoglobin, cholesterol, creatinine, receptor-binding, tumor size, etc.). Food trials tend to be more pragmatic, with more exploratory designs than drug trials. Food trials tend to use more subjective measures (like satiety/hunger, energy level, quality of life) than drug trials because the food mechanisms of action and causes/effects are only loosely associated with the food.

Foods are part of everyday life and food trials are designed closer to “real-life” situations than typical drug trials which tend to be more highly and more carefully controlled and more costly (as a result). In addition, food trials:

1. Have greater heterogeneity than drug trials-foods are offered as part of a whole diet within multiple diet experiences.
2. Need valid, reliable and accurate, scientific endpoints which provide sensitive, specific, and predictive value. These endpoints should be available and practical for widespread applications.
3. Are lower risk trials than drug trials (since the food is not a highly purified chemical with directed/specific/known drug effect and expected side effects; food has smaller, more diverse and more subtle health effects with a lower risk of adverse side effects, but foods are consumed by a larger population)

For successful food-related health claims, the specific food mentioned in the claim must be the test article in the adequately powered and controlled clinical trial/s. Robust evidence (including appropriate endpoints and biomarkers) must be provided to show the beneficial physiological effects in the specific target population [22].

Good science relies on multiple types of exploration and scientific reasoning. A single clinical trial (even a large randomized, double-blind, placebo-controlled clinical trial) only provides a part of the required scientific knowledge (even when multiple endpoints are explored). One clinical trial is limited in time, in the population studied and even in the product applied. Good science puts many different bits of scientific knowledge together to generate or strengthen hypotheses and to test ideas and continue exploring the truth. The correct trial type should be used for the specific product

and question being asked.

## Acknowledgements

### Funding and Sponsorship

Funding support was provided by Glanbia Nutritionals; however, Glanbia Nutritionals was not involved in the design, development, revision or any other aspect of this manuscript.

### Contributions of others

Thanks to the Alimentix team: Kaitlin Cady, Tyler Foutch, Anthony O'Neil, and Dr. Lindsay Young for background research and literature searching for this manuscript. Dr. Young also provided assistance completing the editorial revisions requested by peer-reviewers as assigned and managed by the journal editor.

### Declaration of interest

Dr. Frestedt declares no conflict of interest for this publication. Alimentix, the Minnesota Diet Research Center conducts food-related clinical trials and is a wholly owned subsidiary of Frestedt Incorporated which provides global consulting services regarding clinical research, regulatory negotiations and quality system developmental activities for foods, drugs, medical devices and other types of products.

## References

1. Carlisle R. Scientific American Inventions and Discoveries. New Jersey. John Wiley & Sons, Inc. 2004; 393.
2. AbuMweis SS, Jew S, Jones PJH. Optimizing clinical trial design for assessing the efficacy of functional food. *Nutr Rev*. 2010; 68: 485-99.
3. Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods. *Br J Nutr*. 2011; 106: S3-15.
4. Agriculture and Agri-Food Canada: Best Practices for Food-Based Clinical Trials Guidance for Planning, Conducting and Reporting on Human Studies to Support Health Claims. Ottawa: Minister of Agriculture and Agri-Food Canada. 2013.
5. O'Connor EM. Clinical trials for foods and supplements: Guidance for industry symposium report. *Nutrition Bulletin*. 2013; 38: 262-268.
6. Anderson ML, Griffin J, Goldkind SF, Zeitler EP, Wing L, Al-Khatib SM, et al. The Food and Drug Administration and pragmatic clinical trials of marketed medical products. *Clin Trials*. 2015. 12: 511-519.
7. 103<sup>rd</sup> US Congress. Public Law 103-417: Dietary Supplement Health and Education Act. 1994.
8. FDA. Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r) of the Federal Food, Drug, and Cosmetic Act. 2008.
9. FTC. Advertising FAQ's: A Guide for Small Business.
10. FDA. Substantiation for structure/function claims made in infant formula labels and labeling: guidance for industry. 2016.
11. Onvani S, Haghighatdoost F, Surkan PJ, Azadbakht L. Dairy products, satiety and food intakes: A meta-analysis of clinical trials. *Clin Nutr*. 2016; 1-10.
12. FDA. Dietary Supplements: New dietary ingredient notifications and related issues: Guidance for industry. 2016.
13. FDA. Guidance for Industry: Questions and Answers about the Petition Process. 2011.
14. FDA. “Everything Added to Food in the United States (EAFUS).
15. FDA. “Summary of Qualified Health Claims Subject to Enforcement Discretion”.

16. Sertkaya A, Wong HH, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the US. *Clin Trials*. 2016; 13: 117-126.
17. Neiberg O. Clinical trial tips to win an EFSA health claim. 2013.
18. Yao CK, Gibson PR, Shepherd SJ. Design of clinical trials evaluating dietary interventions in patients with functional gastrointestinal disorders. *Am J Gastroenterol*. 2013; 108: 748-758.
19. FDA. Guidance for Industry. Botanical Drug Development. 2016.
20. Wang JE. FDA Regulatory Requirements for Botanical INDs. *Regulatory Focus*. 2009: 37-41.
21. Younesi E, Ayseli MT. An integrated systems-based model for substantiation of health claims in functional food development. *Trends Food Sci Technol*. 2015; 41: 95-100.
22. Gallagher AM, Meijer GW, Richardson DP, Rondeau V, Skarp M, Stasse-Wolthuis M, et al. A standardized approach towards proving the efficacy of foods and food constituents for health CLAIMs (PROCLAIM): providing guidance. *Br J Nutr*. 2011; 106: S16-S28.