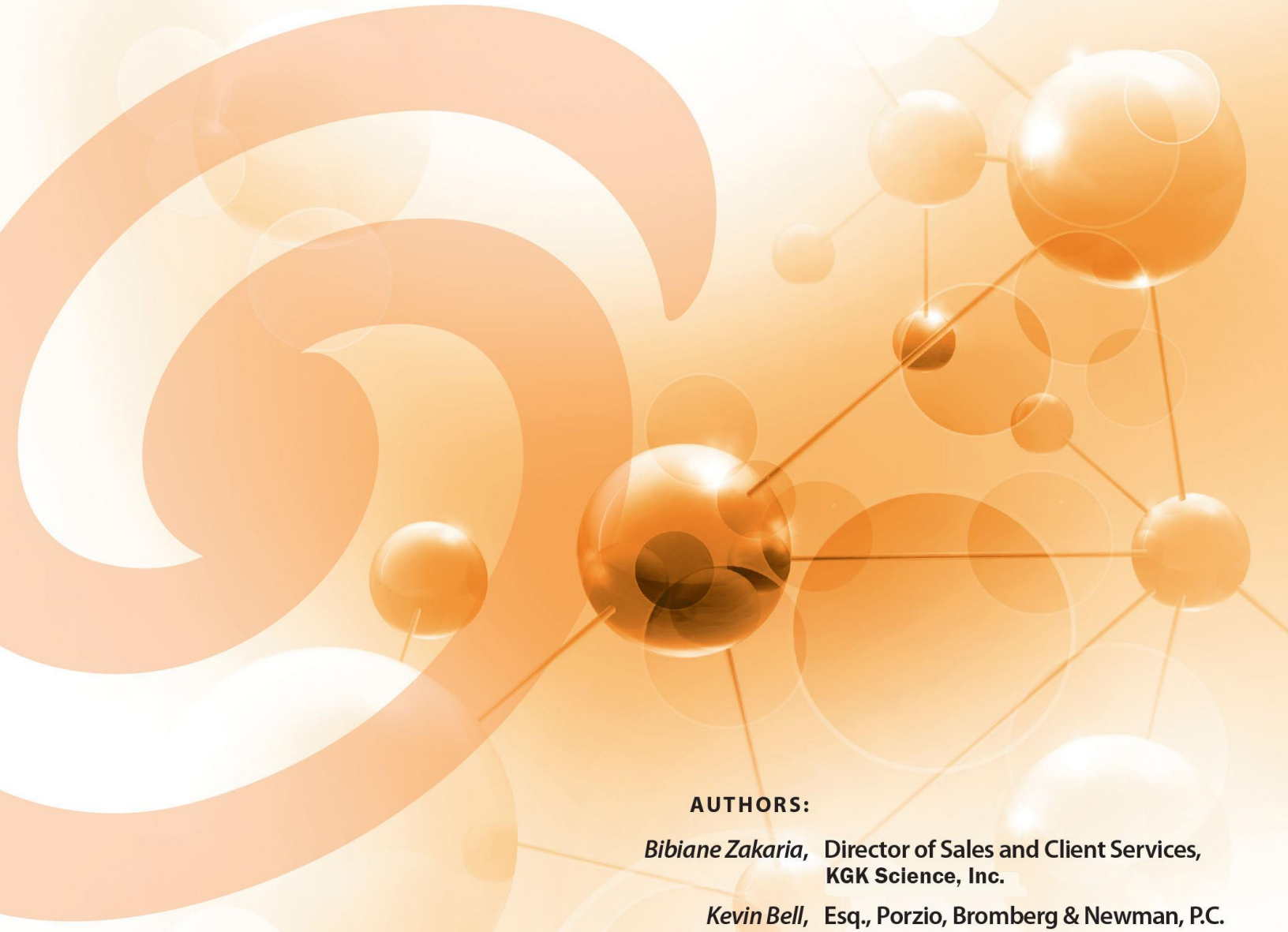
AVOIDING A REGULATORY NIGHTMARE:

Study Endpoints and Claims Substantiation for Clinical Trials



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Synopsis

Conducting clinical trials on your product is an important opportunity to distinguish your product from others. If the study is conducted properly, the results should supply the support you need for your claim statements. In designing your study, it is important to distinguish between clinical endpoints appropriate for dietary supplements from those for drugs. The study must be designed with your target market in mind and for dietary supplements the consumers are those with parameters with the range of normal.

The clinical study should support claim statements that are in compliance with FDA & FTC guidelines. The FDA has primary responsibility for overseeing claims made on dietary supplement labeling, while the FTC has primary responsibility for claims in advertising. However the two organizations often work together. As the above examples have shown, the FTC has been aggressive in taking action against companies it considers to be making advertising claims it considers to be out of compliance. The court decisions in these cases will influence the dietary supplement marketplace going forward. Thus the importance of having clinical evidence to support your product will only increase.

Consider carefully the design of your clinical trial using guidance such as that given above and you will obtain documentation to distinguish your product from others while supplying the support you need for your claim statements.

Thinking of a clinical study to demonstrate efficacy of your product?

We discuss points for producing a successful clinical trial

- → Dietary supplements require clinical endpoints different from those for drugs.
- → Know your target market and what you are looking to achieve with your study.
- → Define and describe the population intended to benefit from your product.
- → Focus on structure/function endpoints for substantiating structure function claims.
- → How can the study support claim statements that are in compliance with FDA & FTC guidelines?

Introduction

Conducting a clinical trial in the health nutrition industry can be an important step towards boosting the reputation and sales of your dietary supplement product. A clinical study can be the greatest investment a company can make in a product. But - where to start? What are the potential pitfalls? The FDA and FTC have made news headlines with their regulatory activities, including large fines for companies and individuals for unsupported or inappropriate claims. Inappropriately designed clinical studies with dietary supplements can lead to inferences of drugs claims, resulting in a regulatory nightmare.

To set your clinical trial up for success, there are key factors that need to be addressed. Having the right study design offers your trial the best chance to support or substantiate your structure/function claims or health claims.

In this paper we cover the regulatory requirements from the Food and Drug Administration (FDA) and Federal Trade Commission (FTC), focusing on the FTC's new stance on Randomized Clinical Trials (RCTs). We will cover the requirements for support of structure/function on claims that you need to know prior to putting your product on the market. If you are considering a clinical study on your product, we will help you to successfully design that study so that it produces the appropriate endpoints required to produce substantiation for your product claims.

Setting Your Objectives

It is important to define your scientific and marketing goals prior to designing the clinical trial. Define the intended use for your product, along with the target population and the claim statements you want to use to reach that population. For example, if you targeting people concerned about developing osteoarthritis due to wear and tear, then your target population would likely be both men and women from middle age to advancing years. And, a product intended for relieving stress might be targeted towards working mothers.

Important points to consider before designing your clinical study:

- ✓ What are the desired claim statements for the product?
- ✓ What is the target population for this product?
- ✓ Are you interested in demonstrating efficacy, safety or bioavailability?
- ✓ Do you want to start with a pilot study (using small number of participants) or conduct a larger, more definitive trial?
- ✓ Would you benefit from demonstrating efficacy in a clinical trial with structure/function endpoints first followed later by a clinical study developed to substantiate a health or qualified health claim petition to FDA?
- ✓ What is the best study design? Examples include open label, double-blind, randomized, placebo control, parallel and cross-over designs.
- ✓ Will the study need a run-in period to establish a baseline before it starts?
- ✓ What is the appropriate control? How can the placebo be made similar enough to the test product to ensure blinding?

Clinical Studies for Marketing and Claim Substantiation

Once your product indication and target population have been defined, it is time to consider the regulatory framework within which your product will be sold. Governmental authorities in the US that regulate claims for dietary supplements include the US Food and Drug Administration (FDA) and the Federal Trade Commission (FTC). The Office of Inspector General (OIG) has an oversight role, extending to programs under the FDA and other agencies in the Department of Health and Human Services (HHS). Navigating the requirements set by these agencies can be complicated and confusing. This paper focuses

on guidance these regulatory bodies have provided regarding allowable claims and the substantiation of those claims.

DIETARY SUPPLEMENT CATEGORY ESTABLISHED BY DSHEA

The category of dietary supplements and its regulatory framework was created through the passage of the Dietary Supplement Health and Education Act (DSHEA) by the US Congress in 1994[1]. This law defines a dietary supplement as a product that is ingested by mouth to supplement the diet and contains one or more of the following ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or a concentrate, a metabolite, a constituent, or an extract.

DIETARY SUPPLEMENT CLAIMS

The FDA has primary responsibility for overseeing claims made on dietary supplement labeling. Labeling includes any display of written, printed or graphic matter upon the container, wrapper or accompanying material, as well as web sites.[2] Among the allowable and most commonly used claims for dietary supplements are nutrient content claims, health claims, and structure/function claims. The FDA regulates each of these types of claims differently.

NUTRIENT CONTENT CLAIMS describe the level of a nutrient in a dietary supplement or other food (e.g., "200 mg of folic acid," "good source of vitamin C", "low fat," or "high fibre".)

HEALTH CLAIMS describe a relationship between a food, or food component (including a dietary supplement ingredient), and reduced risk of a disease or health-related condition. "Adequate calcium throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis" is an example of a health claim.

STRUCTURE/FUNCTION CLAIMS describe the role of a dietary supplement in the structure and function of human bodies, but the claims may not explicitly or implicitly claim to prevent, treat, mitigate, cure, or diagnose a disease. A structure/function claim may claim a benefit related to a classical nutrient deficiency disease (e.g., scurvy) as long as it discloses the prevalence of such disease in the United States. A structure function claim may characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function. It may also describe general well-being from consumption of a nutrient or dietary ingredient.

DSHEA requires manufacturers to meet three requirements for placing a structure/function claim on a supplement label: (1) substantiation that the claim is truthful and not misleading, (2) notification to FDA within 30 days of marketing the supplement with the claim, and (3) a disclaimer on the supplement label.[3]

Regulation of Claim Statements by FDA and FTC

[1] Public Law 103-47 § 3 (codified at 21 U.S.C. § 32 (ff)(1)). http://ods.od.nih.gov/About/DSHEA_Wording.aspx
[2] FDA Dietary Supplements. http://www.fda.gov/Food/DietarySupplements/
[3] 21 U.S.C. § 343 (r)(6)

Under DSHEA, the US Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) have shared jurisdiction over substantiation of structure/function claims.

The FDA's Center for Food Safety and Applied Nutrition has primary responsibility for overseeing claims made on dietary supplement product labeling, including packaging, inserts and other promotional materials distributed at the point of sale. Marketing on the Internet is subject to regulation in the same fashion as promotions through any other media. Therefore, social media and websites where a firm's supplements can be purchased are also considered labeling, in accordance with Section 201(m) [21 U.S.C. 321(m)] of the Federal Food, Drug, and Cosmetic Act.

The FTC has primary responsibility for claims in advertising, including print and broadcast ads, infomercials, catalogues, and similar direct marketing materials. The FTC enforces laws that are designed to ensure that consumers get accurate information about dietary supplements so that they can make informed decisions about these products.

The FTC and FDA will often work together, under a long-standing liaison agreement governing the on enforcement activities related to dietary supplements. Lawyers working in the industry have noted a growing increase in collaboration between the two agencies.[4] For example, on February 1, 2011, FDA issued a warning letter to a dietary supplement maker alleging that certain claims on the company's website constituted unauthorized disease claims, which also caused the dietary supplement products to be unapproved drugs. In the warning letter, FDA cited FTC advertising standards as a further basis for challenging the company's conduct. While the FTC was not a signatory of the letter, the letter requested that the company respond to the FTC regarding the potential violations of the FTC Act.

OIG

The role of the Office of Inspector General (OIG) is to protect the integrity of the Department of Health and Human Services (HHS) programs, as well as the health and welfare of beneficiaries served by those programs.[5] This statutory mission is carried out through a nationwide network of audits, investigations, and inspections. OIG's oversight extends to programs under other HHS institutions, including the Centers for Disease Control and Prevention, National Institutes of Health, and the Food and Drug Administration.

The OIG has produced 2 reports on Dietary supplements. The first report in 2003 focused on dietary supplement labels with the goal of providing suggestions that might better assist the consumer to make more informed and appropriate choices about supplement use.[6] The second report in 2012 focused on structure/function claims and found that the industry largely failed to meet federal requirements.[7]

STRUCTURE/FUNCTION CLAIMS

In January of 2000, the FDA published a final rule in the Federal Register defining the types of statements that may be used on the label and in the labeling of dietary supplements without prior review by the

[4] Villa Franco, JE & colleagues. Nutritional Outlook May 2011, 32-35
[5] OIG About Us. https://oig.hhs.gov/about-oig/about-us/index.asp
[6] Dietary Supplement Labels: Key Elements. OEI-01-01-00120. March 2003. http://oig.hhs.gov/oei/reports/oei-01-01-00120.pdf
[7] Dietary supplements: Structure/function Claims Fail to Meet Federal Requirements. OEI-01-11-00210. Oct 2012. http://oig.hhs.gov/oei/reports/oei-01-11-00210.asp

agency.[8] Called structure/function claims, these claims are statements that describe the effect a dietary supplement may have on the structure or function of the body. The final rule provides guidance in determining when a statement is a disease claim or a structure/function claim. If a product is described as assisting in the diagnosis, mitigation, treatment, cure, or prevention of a disease it is considered as making a disease claim on a dietary supplement. The consequences are that the product will be charged as an unapproved new drug under the Federal Food, Drug, and Cosmetic Act until the claim is removed or qualified to an acceptable structure function claim for a dietary supplement.

In an example given by the FDA report, a dietary supplement may not claim that it "prevents or treats cancer," "reduces pain associated with arthritis," or "relieves bronchospasms" (which would imply treatment of a disease because bronchospasms are a symptom of asthma).

In another example, a supplement may claim that it "curbs appetite to help with weight loss," but it may not claim to "aid weight loss to treat obesity" because obesity is a disease. Similarly, a supplement may claim to "support immunity," but may not claim to "boost the immune system against colds and flu" because the latter references specific diseases.

The FDA defines disease as: ...damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension); except that diseases resulting from essential nutrient deficiencies (e.g., scurvy, pellagra) are exempt from the definition of disease in 21 CFR 101.93(g).[9]

If FDA considers that the label of a product marketed as a dietary supplement contains a disease claim, it will treat the product as an unapproved drug and may take enforcement action against the manufacturer or distributor. Actions may include issuing a warning letter, seizing the product, seeking criminal prosecution, or prohibiting the sale of the product through an injunction.

SUBSTANTIATION OF STRUCTURE/FUNCTION CLAIMS

Manufacturers must have substantiation for the structure/function claims on their products' labels to ensure that they are truthful and not misleading. In any legal proceeding concerning structure/function claims, FDA must prove that the claim is false or misleading. However, DSHEA does not require manufacturers to submit the substantiation to FDA to determine its adequacy, and FDA has no legal authority to compel manufacturers to produce substantiation upon request. Therefore, FDA has limited authority to enforce the substantiation requirement.

FDA has published guidance on the extent and nature of substantiation that manufacturers should have to comply with the law.[10] In general, FDA recommends that evidence be derived primarily from human studies that use widely accepted scientific methods. The guidance also lists types of background

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[8] Federal Register: Jan 6, 2000, 65 (4), 999-1050 http://www.fda.gov/ohrms/dockets/98fr/010600a.txt

[9] http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm103340.htm

[10] FDA, Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug and Cosmetic Act, December 2008. http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm073200.htm

information—such as in vitro or animal studies, meta-analyses, and review articles—that manufacturers may use to substantiate claims. However, the guidance notes that background information, when used alone, may not be adequate to substantiate claims.

FDA uses a standard of "competent and reliable scientific evidence" for substantiation. To meet this standard, FDA recommends that manufacturers consider the following when substantiating structure/function claims:

THE RELATIONSHIP OF THE EVIDENCE TO THE CLAIM: The evidence should demonstrate a direct effect of the supplement on a structure or function of the body in a population similar to that which will be consuming the product. The evidence should test either the product itself or an amount and potency of the active ingredients that are similar to the product.

THE TOTALITY OF THE EVIDENCE: Manufacturers should consider the total body of evidence—both favourable and unfavourable—in determining whether it is adequate to substantiate a claim. If evidence conflicts or shows inconsistent results, it will raise questions about whether a structure/function claim is substantiated.

THE QUALITY OF THE EVIDENCE: Manufacturers must consider the scientific quality of studies used to substantiate claims. FDA considers human studies that are randomized, double-blind, parallel group, placebo-controlled trials that focus on a representative population to be the "gold standard" for substantiation. Manufacturers may use other human or nonhuman studies to substantiate claims, but should consider factors in the studies' methods that may affect the results.

THE MEANING OF THE CLAIM(S) BEING MADE: Manufacturers should have substantiation for each possible interpretation of a structure/function claim. For example, a supplement may claim to "promote weight loss." If the manufacturer's evidence is a study showing that the supplement's main ingredient temporarily increases metabolism, but not showing actual weight loss, then the manufacturer has not accounted for the meaning of the claim in its substantiation.

FTC

The FTC requires that advertising must be truthful and not misleading; and before disseminating an ad, advertisers must have adequate substantiation for all objective product claims.[11] The FTC considers a deceptive ad to be one that contains a misrepresentation or omission that is likely to mislead consumers to their detriment. When evaluating claims about the efficacy and safety of foods, dietary supplements and drugs, the FTC applies a substantiation standard of competent and reliable scientific evidence.

EXPRESS AND IMPLIED CLAIMS

[11] FTC: Dietary Supplements: An Advertising Guide for industry. Bureau of Consumer Protection. 1998 https://www.ftc.gov/tips-advice/business-center/guidance/dietary-supplements-advertising-guide-industry

The FTC considers all claims that are made directly as well as those suggested or implied by the advertisement. The "net impression" conveyed by the ad includes the text, the product name, and the depictions. If an ad lends itself to more than one reasonable interpretation, the FTC considers the advertiser to be responsible for substantiating each interpretation. Once the claims are identified, the scientific evidence is assessed to determine whether there is adequate support for those claims.

The FTC acknowledges that a statement about a product's effect on a normal "structure or function" of the body may also convey to consumers an implied claim that the product is beneficial for the treatment of a disease. If elements of the ad imply that the product also provides a disease benefit, the advertiser must be able to substantiate the implied disease claim even if the ad contains no express reference to disease.

In an example given in the FTC's guidance document, an ad for an herbal supplement makes the claim that the product boosts the immune system to help maintain a healthy nose and throat during the winter season. The ad features the product name "Cold Away" and includes images of people sneezing and coughing. The various elements of the ad — the product name, the depictions of cold sufferers, and the reference to nose and throat health during the winter season — likely convey to consumers that the product helps prevent colds. Therefore, the advertiser must be able to substantiate that claim. Even without the product name and images, the reference to nose and throat health during the winter season may still convey a cold prevention claim.

SUBSTANTIATING CLAIMS

The FTC states that there must be a reasonable basis for all express and implied claim statements. What constitutes a reasonable basis depends greatly on what claims are being made, how they are presented in the context of the entire ad, and how they are qualified. The FTC considers the following factors:

THE TYPE OF PRODUCT

Generally, products that are related to consumer health or safety require a relatively high level of substantiation.

THE TYPE OF CLAIM

Claims that are difficult for consumers to assess on their own are held to a more exacting standard. Examples include health claims that may be subject to a placebo effect or technical claims that consumers cannot readily verify for themselves.

THE BENEFITS OF A TRUTHFUL CLAIM, AND THE COST/FEASIBILITY OF DEVELOPING SUBSTANTIATION FOR THE CLAIM

These factors are often weighed together to ensure that valuable product information is not withheld from consumers because the cost of developing substantiation is prohibitive. This does not mean, however, that an advertiser can make any claim it wishes without substantiation, simply because the cost of research is too high.

THE CONSEQUENCES OF A FALSE CLAIM

The consequence of a false claim includes physical injury. For example, physical injury can result if a consumer relies on an unsubstantiated claim about the therapeutic benefit of a product and foregoes a proven treatment. Economic injury as a consequence of a false claim is also considered.

THE AMOUNT OF SUBSTANTIATION EXPERTS IN THE FIELD BELIEVES IS REASONABLE

In making this determination, the FTC gives great weight to accepted norms in the relevant fields of research and consults with experts from a wide variety of disciplines, including those with experience in botanicals and traditional medicines. Where there is an existing standard for substantiation developed by a government agency or other authoritative body, the FTC accords great deference to that standard.

The FTC typically requires claims about the efficacy or safety of dietary supplements to be supported with "competent and reliable scientific evidence," defined in FTC cases as "tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results." This is the same standard the FTC applies to any industry making health-related claims. There is no fixed formula for the number or type of studies required or for more specific parameters like sample size and study duration. There are, however, a number of considerations to guide an advertiser in assessing the adequacy of the scientific support for a specific advertising claim.

EXPRESS AND IMPLIED CLAIMS

If an advertiser asserts that it has a certain level of support for an advertised claim, it must be able to demonstrate that the assertion is accurate. Therefore, advertisers must have the level of support that they claim, expressly or by implication, to have.

In an example provided by the FTC, an advertisement for a vitamin supplement claims that 90% of cardiologists regularly take the product. In addition to the literal claim about the percentage of cardiologists who use the product, the ad likely conveys an implied claim that the product offers some benefit for the heart. Therefore, the advertiser must have adequate support for both representations.

THE AMOUNT AND TYPE OF EVIDENCE

When no specific claim about the level of support is made, the evidence needed depends on the nature of the claim. The FTC considers all forms of competent and reliable scientific research when evaluating substantiation, but a well-controlled human clinical study is viewed as the most reliable form of evidence. There are no requirements for a specific number of studies, but replication of research results adds to the weight of the evidence.

Results obtained in animal and/or in vitro studies are considered supportive where they are generally considered to be acceptable substitutes for human research or where human research is infeasible.

In an example provided in the FTC report, an advertiser relies on animal and in vitro studies to support a claim that its vitamin supplement is more easily absorbed into the bloodstream than other forms of the vitamin. However, the animal research uses a species of animal that, unlike humans, is able to synthesize the vitamin, and the in vitro study uses a different formulation with a higher concentration of the compound than the product being marketed. In addition, human research is feasible and relatively inexpensive to conduct in light of the potential sales of the product and is the type of research generally accepted in this particular field of study. The substantiation is likely to be inadequate in this case, both because there are significant methodological problems and because, in this particular instance, human research is both feasible and the accepted approach in the field.

Epidemiologic evidence may be an acceptable substitute for clinical data, especially in the case of a relationship between a nutrient and a condition that may take decades to develop. Epidemiologic evidence may be supported by research explaining the biological mechanism underlying the claimed effect.

The FTC does not consider anecdotal evidence to be supportive documentation. Even if those experiences are genuine, they could be attributable to a placebo effect or other factors unrelated to the supplement. In an example provided by the FTC, an advertisement for a supplement claims that the product will cause dramatic improvements in memory and describes the experiences of 10 people who obtained these results. The descriptions of these anecdotal experiences are truthful, but the advertiser has no scientific substantiation for the effect of its product on memory and cannot explain why the product might produce such results. The FTC considers that individual experiences are not considered adequate to substantiate the claim without confirming scientific research.

THE QUALITY OF THE EVIDENCE

The FTC considers the internal validity of each piece of evidence. The design, implementation, and results of each piece of research are considered in assessing the adequacy of the substantiation. The FTC does not have a set protocol for how to conduct research, but considers principals generally accepted in the scientific community. For example, scientists consider that a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist. A study of longer duration may also reveal more information regarding the safety of the product. The FTC also considers evidence of a dose-response relationship (i.e., the larger the dose, the greater the effect) or a recognized biological or chemical mechanism to explain the effect. The FTC looks for demonstration of statistical significance of the findings. A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of placebo effect or chance. The results should translate into a meaningful benefit for consumers. Some results that are statistically significant may still be so small that they would mean only a trivial effect on consumer health.

The nature and quality of the written report of the research are important. Research cannot be evaluated accurately on the basis of an abstract or an informal summary. The FTC does not require that studies be published and will consider unpublished, proprietary research. However, the publication of a peer-reviewed study in a reputable journal indicates that the research has received some measure of scrutiny. The study must be of good quality and publication does not necessarily mean that such research is conclusive evidence of a substance's effect.

In an example provided by the FTC, a marketer of an herbal supplement claims that its product promotes healthy vision and is approved in Germany for this purpose. The product has been used extensively in Europe for years and has obtained approval by the German governmental authorities, through their monograph process, for use to improve vision in healthy people. The company has two abstracts of German trials that were the basis of the German monograph, showing that the ingredient significantly improved the vision of healthy individuals in the test group over the placebo group. Animal trials done by the company suggest a plausible mechanism to explain the effect. Although approval of the supplement under the German monograph suggests that the supplement is effective, advertisers should still examine the underlying research to confirm that it is relevant to the advertiser's product (for example, that the dosage and formulation are comparable) and to evaluate whether the studies are scientifically sound. Advertisers should also examine any other research that exists, either supporting or contradicting the monograph, especially if it is not possible to identify and review the research on which the monograph is based.

THE TOTALITY OF THE EVIDENCE

The FTC considers all relevant research relating to the claimed benefit of their supplement: both with positive and negative results. Wide variation in the outcomes of studies, inconsistent or conflicting results raise questions about the substantiation of a claim. Where there are inconsistencies in the evidence, it is important to examine whether there is a plausible explanation for those inconsistencies. In some instances, for example, the differences in results are attributable to differences in dosage, the form of administration (e.g., oral or intravenous), the population tested, or other aspects of study methodology.

In another example provided by the FTC, an advertiser wishes to make the claim that a supplement product will substantially reduce body fat. The advertiser has two controlled, double-blind studies showing a modest but statistically significant loss of fat at the end of a six-week period. However, there is an equally well-controlled, blinded 12-week study showing no statistically significant difference between test and control groups. Assuming other aspects of methodology are similar, the studies taken together suggest that, if the product has any effect on body fat, it would be very small. Given the totality of the evidence on the subject, the claim is likely to be unsubstantiated.

THE RELEVANCE OF THE EVIDENCE TO THE SPECIFIC CLAIM

The FTC reminds advertisers that they must make sure that the research on which they rely is not just valid, but must also be relevant to the specific product being promoted and to the specific benefit being advertised. Advertisers should ask questions such as: How does the dosage and formulation of the advertised product compare to what was used in the study? Does the advertised product contain additional ingredients that might alter the effect of the ingredient in the study? Is the advertised product administered in the same manner as the ingredient used in the study? Does the study population reflect the characteristics and lifestyle of the population targeted by the ad? If there are significant discrepancies between the research conditions and the real life use being promoted, advertisers need to evaluate whether it is appropriate to extrapolate from the research to the claimed effect.

In drafting ad copy, the advertiser should take care to make sure that the claims match the underlying support. Claims that do not match the science, no matter how sound that science is, are likely to be unsubstantiated.

As an example, several clinical trials have been done on a specific botanical extract showing consistently that the extract is effective for supporting the immune system. The studied extract is a complex combination of many constituents and the active constituents that may produce the benefit are still unknown. An advertiser wishes to cite this research in its advertising, as proof that its product will support the immune system. The advertiser's product is made using a different extraction method of the same botanical. An analysis of the extract reveals that it has a significantly different chemical profile from the studied extract. The advertiser should not rely on these clinical trials alone as substantiation because the difference in extracts may result in significant differences in the two products' efficacy.

THIRD PARTY LITERATURE

Dietary supplement advertisers should be aware that the use of newspaper articles, abstracts of scientific studies, or other "third party literature" to promote a particular brand or product can have an impact on how consumers interpret an advertisement and on what claims the advertiser will be responsible for substantiating. For purposes of dietary supplement labeling, Section 5 of DSHEA provides an exemption from labeling requirements for scientific journal articles, books and other publications used in the sale of dietary supplements, provided these materials are reprinted in their entirety, are not false or misleading, do not promote a specific brand or manufacturer, are presented with other materials to create a balanced view of the scientific information, and are physically separate from the supplements being sold. If a balanced view of the scientific information is not provided, even claims made from third party literature can be reviewed for making disease claims as evidence of intent of the product (unapproved new drug v. dietary supplement).

The FTC will generally follow an approach consistent with the labeling approach when evaluating the use of such publications in other contexts, such as advertising. Although the FTC does not regulate the content or accuracy of statements made in independently written and published books, articles, or other non-commercial literature, FTC law does prohibit the deceptive use of such materials in marketing products. The determination of whether the materials will be subject to FTC jurisdiction turns largely on whether the materials have been created or are being used by an advertiser specifically for the purpose of promoting its product.

The FTC has taken action not just against supplement manufacturers, but also, in appropriate circumstances, against ad agencies, distributors, retailers, catalogue companies, infomercial producers and others involved in deceptive promotions. Therefore, all parties who participate directly or indirectly in the marketing of dietary supplements have an obligation to make sure that claims are presented truthfully and to check the adequacy of the support behind those claims.

FTC Actions

FTC V. POM WONDERFUL – 2015

In September 2010, the FTC charged that the marketers of POM Wonderful 100% Pomegranate Juice and POMx supplements made false and unsubstantiated claims that their products will prevent or

treat heart disease, prostate cancer, and erectile dysfunction.[12] FTC alleged that POM Wonderful LLC, sister corporation Roll International Corp., and principals Stewart Resnick, Lynda Resnick, and Matthew Tupper violated federal law by making deceptive disease prevention and treatment claims. The ads in question appeared in national publications such as Parade, Fitness, The New York Times, and Prevention magazines; on Internet sites such as pomtruth.com, pomwonderful.com, and pompills.com; on bus stops and billboards; in newsletters to customers; and on tags attached to the product.

The FTC complaint alleges that POM Wonderful's heart disease claims are false and unsubstantiated because many of the scientific studies conducted by POM Wonderful did not show heart disease benefit from use of its products. It alleges that the prostate cancer claims are false and unsubstantiated because, among other reasons, the study POM Wonderful relied on was neither "blinded" nor controlled. Finally, it alleges that the erectile dysfunction claims are false and unsubstantiated because the study on which the company relied did not show that POM Juice was any more effective than a placebo.

This case has been on going in the courts for the past 5 years. In January 2015, the US Court of Appeals in the District of Columbia agreed with the FTC that the company must have competent and reliable scientific evidence to support label claims.[13] The court upheld the assertion that because POM's claims on its products were not based on randomized controlled trials they were therefore false and misleading. The FTC had stated that two such clinical trials were required. However the court disagreed and found that one such study would be sufficient to support the sorts of claims made by POM.

US V. BAYER CORP., US DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY - 2014

In September of 2014 the US Department of Justice, on behalf of the FTC, filed a motion holding Bayer in contempt of a 2007 consent order that required Bayer to possess "competent and reliable scientific evidence" for dietary supplement claims.[14] The 2007 consent order was the outcome of FTC complaints against Bayer alleging that the company made weight-loss and weight-control claims that were not supported by competent and reliable scientific evidence.[15] Bayer paid $25 million to settle allegations of deceptive marketing for Xenadrine EFX, CortiSlim, TrimSpa, and One-A-Day WeightSmart. The company also agreed not to make any unsubstantiated representations regarding benefits, performance, efficacy, safety or side effects of any dietary supplement, multivitamin or weight control product.

The case filed in 2014 was regarding claims made for a probiotic dietary supplement called Phillip's Colon Health. The claims made for the product include prevention of constipation, diarrhea, gas and bloating. The Justice Department attorneys argued that the claims imply that the product can prevent, cure or treat symptoms of gastrointestinal distress. The feds maintained that, given the claims made for

[12] FTC Docket # 9344. https://www.ftc.gov/sites/default/files/documents/cases/2010/09/100927admincmplt.pdf
[13] FTC Jan 30, 2015. https://www.ftc.gov/news-events/press-releases/2015/01/statement-ftc-chairwoman-edith-ramirez-appellate-ruling-pom
[14] US Department of Justice, Sep 12, 2014. http://www.justice.gov/opa/pr/united-states-seeks-civil-contempt-against-bayer-corporation-failure-substantiate-promotional
[15] FTC Press Release Jan 4, 2007. https://www.ftc.gov/news-events/press-releases/2007/01/federal-trade-commission-reaches-new-years-resolutions-four-major

Phillips' Colon Health, Bayer should have conducted randomized, placebo-controlled clinical trials. They also stated that none of nearly 100 documents that Bayer provided to the FTC validated its claims.

The FTC is seeking a contempt-of-court order against Bayer, according to documents filed in federal court in Newark, New Jersey. The FTC further commented that, 'Bayer repeatedly advertises Phillips' Colon Health along with Phillips' Milk of Magnesia, a laxative, and Phillips' Stool Softener, both of which are familiar over-the-counter drugs. Bayer has advertised that Phillips' Colon Health is 'on the shelf near your other trusted Phillips' products,' " according to the brief. "The obvious implication of such advertisements is that a consumer should think of Phillips' Colon Health as being in the same category as two of Bayer's gastrointestinal over-the-counter drugs, which, as drugs, are indicated to prevent, cure, or treat disease. Bayer advertised Phillips' Colon Health in this manner even though it was well aware that the majority of Americans do not know how probiotics work or think that probiotics work the same as laxatives or antacids."

Bayer maintains that probiotic bacteria, including the three species used in its product, have a "long and well-documented safety record, complemented by volumes of human clinical studies on their digestive benefits.[16] It is this research upon which Bayer has legitimately based all of our claims, which include the fact that the product will 'promote overall digestive health' and 'help defend against occasional constipation, diarrhea, and gas and bloating.'" Bayer disputes the notions that Phillips' Colon Health should be used to mitigate, prevent or treat any disease; that clinical trials are needed to substantiate any claims since these are "generally required for drugs" and are not for dietary supplement; and that the 2007 consent decree was even violated. Bayer believes it has the evidence to back up its promotional claims.

FTC ON GREEN COFFEE BEAN WEIGHT LOSS CLAIM - 2014

In 2010, the FTC charged that Duncan and his companies, Pure Health LLC and Genesis Today, Inc., deceptively claimed weight-loss benefits of green coffee bean extract through a campaign that included appearances on The Dr. Oz Show, The View, and other television programs.[17] They claimed that the supplement could cause consumers to lose 17 pounds and 16 percent of their body fat in just 12 weeks without diet or exercise, and that the claim was backed up by a clinical study.

The company's claims were based on a single clinical study which was published in the May 2012 edition of *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, titled *Randomized, double-blind placebo controlled linear dose crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects* and authored by Joe Vinson and colleagues.

The FTC complaint alleged that the study was so hopelessly flawed that no reliable conclusions could be drawn from it. According to the FTC's complaint, the company paid researchers in India to conduct a clinical trial on overweight adults to test whether Green Coffee Antioxidant (GCA), a dietary supplement containing green coffee extract, reduced body weight and body fat. The FTC charged that the study's lead

[16] Daniells, S. Bayer 'extremely disappointed & strongly disagrees' with the FTC/DoJ allegations against Phillips' Colon health claims. NutraIngredients-USA.com. 12 Sep, 2014

[17] FTC May 19, 2014. https://www.ftc.gov/news-events/press-releases/2014/05/ftc-charges-green-coffee-bean-sellers-deceiving-consumers-through

investigator repeatedly altered the weights and other key measurements of the subjects, changed the length of the trial, and misstated which subjects were taking the placebo or GCA during the trial. When the lead investigator was unable to get the study published, the FTC says that AFS hired researchers Joe Vinson and Bryan Burnham at the University of Scranton to rewrite it. Despite receiving conflicting data, Vinson, Burnham, and AFS never verified the authenticity of the information used in the study, according to the complaint.

The FTC found that the study was too small to provide convincing data as it only included 16 subjects. The largest amount of weight loss occurred during the washout periods and the largest weight loss occurred in the placebo group. There was a lack of clarity in the study blinding process and it was undetermined whether or not the participants exercised during the study.

In September 2014, Lindsey Duncan, and the companies he controlled, agreed to settle the FTC charges. Under the settlement deal, the defendants are barred from making deceptive claims about the health benefits or efficacy of any dietary supplement or drug product, and will pay $9 million for consumer redress.

FTC COMPLAINT AGAINST I-HEALTH AND MARTEK - 2014

In June 2014, the FTC charged that i-Health, Inc. and Martek Biosciences made deceptive claims while advertising their BrainStrong Adult dietary supplement.[18] The company claimed that the product, which contains the Omega-3 fatty acid DHA, would improve adult memory and prevent cognitive decline. The complaint also alleges the marketers falsely claimed they had clinical proof that BrainStrong Adult improves adult memory.

In the television ad, a woman forgets why she walked into a room. Through a voice over, her dog tells the audience she is there to find her sunglasses, which are sitting on top of her head. Another voice over then asks, "Need a memory boost? Introducing BrainStrong … Clinically shown to improve adult memory."

The final order bars the companies from claiming that any dietary supplement, food, drug, or product promoted to prevent cognitive decline or improve memory or containing DHA can prevent cognitive decline or improve memory in adults, unless the claim is truthful and supported by clinical testing. It also bars the companies from making claims about the health benefits, performance, safety, or effectiveness of such products, unless the claims are supported by competent and reliable scientific evidence. Finally, the companies cannot claim they have clinical proof when they do not.

FTC V. NESTLE HEALTH CARE NUTRITION - 2010

In July 2010, the FTC filed complaint charges against Nestlé HealthCare Nutrition, Inc. that the company made deceptive claims in television, magazine, and print ads that BOOST Kid Essentials prevents upper respiratory tract infections in children, protects against colds and flu by

[18] FTC June 9, 2014. https://www.ftc.gov/news-events/press-releases/2014/06/supplement-marketers-settle-ftc-charges-brainstrong-adult-memory

strengthening the immune system, and reduces absences from daycare or school due to illness.[19]

BOOST Kid Essentials is a nutritionally complete drink intended for children ages 1 to 13. The probiotics in BOOST Kid Essentials are embedded in a straw that comes with the drink, which was prominently featured in ads for the product. Probiotics are live, beneficial bacteria that are found naturally in many foods, and they are known for aiding digestion and fighting harmful bacteria.

Nestlé's claimed that its probiotic product would prevent kids from getting sick or missing school. The advertisements challenged by the FTC featured the drink's probiotic straw. In one ad, the straw jumped out of the drink box, formed a protective barrier around a girl as she encountered a sneezing boy, and then formed steps allowing her to reach a basketball hoop and shoot a ball into the net.

The FTC charged that the ads falsely claimed that BOOST Kid Essentials is clinically shown to reduce illness in children, to protect from colds and flu by strengthening the immune system, and to help children up to age 13 recover more quickly from diarrhea.

Under the proposed settlement, Nestlé HCN has agreed to stop claiming that BOOST Kid Essentials will reduce the risk of colds, flu, and other upper respiratory tract infections unless the claim is approved by the FDA. Although FDA approval of health claims generally is not required for compliance with the FTC Act, in this case, the FTC determined that requiring FDA pre-approval of claims that certain products prevent or reduce the risk of upper respiratory tract infections will provide clearer guidance. In turn, this will facilitate Nestlé HCN's compliance with the proposed settlement order and will make the order easier to enforce.

Nestlé HCN also has agreed to stop claiming that BOOST will reduce children's sick-day absences and the duration of acute diarrhea in children up to age 13, unless the claims are true and backed by at least two well-designed human clinical studies.

FTC V. IOVATE HEALTH SCIENCES - 2010

The FTC charged Iovate Health Sciences USA and its Canadian parent company, Iovate Health Science Group, Inc. (now known as Kerr Investment Holding Corp.), and a Canadian subsidiary of that company, Iovate Health Sciences, Inc. with deceptively advertising their supplements using television ads, Internet websites, and print ads in national magazines.[20] In July 2010, the company agreed to pay $5.5 million to settle charges that it falsely advertised that its supplements could help consumers lose weight and treat or prevent colds and other illnesses. The $5.5 million was used for refunds to consumers who purchased Accelis, nanoSLIM, and any Cold MD, Germ MD, and Allergy MD product. These supplements were sold over the Internet and were widely available at retail stores. In addition, the settlement requires the marketer to stop making deceptive health claims about the products.

Using photos of white-coated individuals depicted as medical doctors, Iovate's ads claimed that dietary supplements Cold MD and Germ MD treat or prevent colds and flu, and that Allergy MD treats or

[19] FTC Jul 24, 2010. https://www.ftc.gov/news-events/press-releases/2010/07/nestle-subsidiary-settle-ftc-false-advertising-charges-will-drop

[20] FTC Jul 14, 2010. https://www.ftc.gov/news-events/press-releases/2010/07/dietary-supplement-maker-pay-55-million-settle-ftc-false

prevents allergies and hay fever, according to the FTC complaint. Some ads also proclaimed that the products' effectiveness was clinically proven. The FTC complaint alleges that these claims were false and unsubstantiated. The FTC also charged that Iovate falsely advertised that one of the supplements – Allergy MD Rapid-Tabs – was homeopathic.

The Iovate companies also ran ads with deceptive claims that their weight-loss supplements Accelis and nanoSLIM caused weight loss, and were clinically proven to do so, according to the FTC complaint. The ads said consumers could "Lose 32 lbs. FAST" using nanoSLIM, or one to two pounds per week using Accelis. The ads falsely claimed that Accelis was scientifically proven to increase the body's metabolism, and featured testimonials from users claiming they had lost significant amounts of weight, according to the FTC.

Designing Your Clinical Study: Factors to Consider

A carefully designed, well thought out design for your clinical trial is essential to the outcome of the study. Below is a checklist of items to consider along with discussions of important factors to consider.

1. Qualify the scope of your claim
2. Eliminate claims associated with diseases and focus on structure/function statements
3. Using surrogate markers for a disease, explore the upper or lower limits of normal
4. Express the claim within a natural process (e.g. menstrual cycle, eating, vigorous exercise, adolescence, aging)
5. Avoid abnormal conditions associated with a normal process (i.e. benign prostatic hyperplasia or macular degeneration associated with ageing)
6. Use the claim you want to make in a healthy population to guide your study

STUDY POPULATIONS

Target populations for dietary supplements are those who are basically healthy but looking to improve some aspect of their health. By definition dietary supplements are not intended to mitigate, treat, diagnose, prevent, or cure a disease or its symptoms. Dietary supplements are intended to improve health but not treat disease.

One approach for dietary supplements is to address the needs of a healthy population that are concerned about maintaining some aspect of their health. That is, a healthy population that is at the upper limit of normal.

For example, you have a dietary supplement product that could lower blood sugar. But lowering blood sugar would define the product as a drug in treatment of a disease: diabetes. So, a solution might be to focus on the upper range of normal for blood sugar levels (table below). You might also focus on elevations of blood sugar that occur after a meal (post-prandial elevations) as this is a normal process. So, in your study design, do not use people with diabetes, use healthy subjects. If you want to focus on short-term effects, don't use endpoints such as HgA1C, which an indicator of blood sugar levels over the past 3 months. If your initial study shows promising results in healthy volunteers, then you can think about doing the studies necessary to support an authorized health claim.

BLOOD GLUCOSE LEVELS

	Healthy population		Diseased population
	Normal	**Slightly Elevated**	**Diabetes**
Fasting blood glucose	70 to 99 mg/dl (3.9 to 5.5 mmol/L)	100 to 125 mg/dl (5.6 to 6.9 mmol/L)	> 126 mg/dl (7.0 mmol/L)
Glucose tolerance test*	<140 mg/dl (7.8 mmol/L)	140 to 200 mg/dl (7.8 to 11.1 mmol/L)	<200 mg/dl (11.1 mmol/L)

*blood sample drawn 2 hours after administration of beverage containing 75 g glucose

In another example, your portfolio of dietary supplements may include a dietary ingredient or supplement with anti-inflammatory activity as a mechanism of action. This is problematic because claim statements associated with inflammation are not allowed, as it has a role in the body's response to a disease or to a vector of a disease. However you can focus on natural conditions within which inflammation might occur. One such condition is inflammation in muscle tissue after intense workouts. This situation would occur with elite athletes (triathlon competitions, marathon runners and professional sports). Recreational athletes can also over extend themselves. And, in a completely different direction, certain foods might cause a temporary increase in a marker of inflammation. Don't use study subjects who have arthritis as this is a disease condition. For endpoints use clinically-accepted biomarkers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) to measure inflammation. Stay away from other markers associated with disease states such as eicosanoids and cytokines [interleukin 6, tumour necrosis factor (TNF) alpha], acute phase protein serum amyloid A and NF-κB, a protein complex that controls transcription of DNA. Again, if your initial study shows promising results in healthy volunteers, then you can consider the studies necessary to support an authorized health claim.

In other examples, elevated lipid levels and blood pressure might be addressed using dietary supplements before they reach levels associated with significant risk for heart attack and/or stroke.

LDL CHOLESTEROL

LDL Cholesterol Goals and Cut points for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.[21]

Risk Category	**LDL Goal**	**LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)**	**LDL Level at Which to Consider Drug Therapy**
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL

[21] Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) which presents the National Cholesterol Education Program (NCEP) updated recommendations on cholesterol testing and management. http://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference-html

0-1 Risk Factor**	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
** Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

BLOOD PRESSURE[22]

	Healthy		Diseased	
	Normal	Slightly Elevated	Stage I Hypertension	Stage II Hypertension
Systolic	<120 mm Hg	120-139 mm Hg	140-159 mm Hg	≥160 mm Hg
Diastolic	<80 mm Hg	80-89 mm Hg	90-99 mm Hg	≥100 mm Hg

STUDY ENDPOINTS / BIOMARKERS

In a clinical research trial, a clinical endpoint generally refers to the occurrence of a disease, symptom, sign or laboratory test result that constitutes one of the target outcomes of the study. A clinical trial will usually define or specify a primary endpoint as a measure that will be considered success of the therapy (e.g. in justifying a marketing approval). The primary endpoint might be a statistically significant improvement in overall survival. A trial might also define one or more secondary endpoints such as a lack of disease progression. In addition, the study design may include exploratory endpoints that are experimental in nature.

A surrogate endpoint (or marker) is a measure of effect of a certain treatment that may correlate with a real clinical endpoint and is intended to substitute for a clinical endpoint.

In designing a trial to demonstrate effectiveness of a dietary supplement it is important not to select endpoints that could be construed as drug-related.

As an example, a primary endpoint for a product indicated for support of cognition might be working memory, the brain's ability to temporarily store and manage the information required to carry out complex cognitive tasks such as learning, reasoning, and comprehension.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

The number of subjects needed in a clinical study can be determined using statistical analysis based upon the primary endpoint. The analysis can determine the number of subjects likely to produce a statistically significant effect based upon the expected effect of the test agent. This information is best gained from previous studies on this product. If no previous studies are available, an educated guess can usually be made based in previously reported studies using similar agents. The number of participants in the study should be a large enough so that they could be expected to represent the target population as a whole.

[22] American Heart Association: Understanding blood pressure readings. http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp

SAFETY

Along with efficacy, it is also important to show that your product is safe. Safety parameters include blood chemistry profiles such as blood cell counts, the presence of electrolytes, and indicators of kidney and liver function. Any adverse events that occur during the study should be noted even if they do not appear to be related to the test product.

STUDY DESIGN

There are a number of parameters to study design. The optimal study is designed in such a way as to eliminate bias on the part of the researchers and the participants.

A randomized controlled trial (RCT) is one in which the people being studied are randomly allocated one or other of the different treatments. The RCT is the gold standard for a clinical trial. RCTs are often used to test the efficacy or effectiveness of various types of medical interventions and may provide information about adverse effects, such as drug reactions. Random assignment of intervention is done after subjects have been assessed for eligibility and recruited, but before the intervention to be studied begins.

In double-blind studies, neither the participants nor the researchers know which participants belong to the control group or the test group. Random assignment of test subjects to the experimental and control groups is a critical part of any double-blind research design. Only after all the data have been recorded (and in some cases, analyzed) do the researchers learn which participants were in which group. Performing a study in a double-blinded manner is expected to reduce the effects of any preconceived notions or physical cues.

Single-blind describes studies in which the participants do not know which treatment they are receiving, but the experimenters will know.

An open-label trial or open trial is one in which both the researchers and participants know which treatment is being administered. Open-label trials may be appropriate for comparing two very similar treatments to determine which is most effective. An open-label trial may be unavoidable under some circumstances, such as comparing the effectiveness of a medication to intensive physical therapy sessions. An open-label trial may still be randomized. Open-label trials may also be uncontrolled, with all participants receiving the same treatment.

In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study. That is, the treatment is outside the control of the investigator. This type of study is used to provide information on “real world” use and practice. These studies can also provide information on the benefits and risks certain practices in the general population.

RCT’s can be conducted in a parallel fashion or using a cross-over design. In a parallel study, all treatment groups are separately receiving their particular treatment in a concurrent fashion. In a cross-over design, all subjects receive all treatments. They start with one treatment and cross-over to another one during the trial period.

STUDY DESIGN PARAMETERS

→ Study design appropriate for the test agent
- Controls in place for potentially confounding factors

- Randomization of subjects to treatment and control
- Blinding (similarity of test agent and control)

→ Population relevant to the indication of the test agent
- Selected inclusion & exclusion criteria
- Sample size sufficient to show comparative differences

→ Duration of the study appropriate
→ Endpoints selected with consideration of marketing claims
→ Safety parameters included
→ Data collection techniques
→ Results analysis
→ Final report / publication

STUDY PROTOCOL

The clinical protocol should be written according to guidelines provided by the ICH (The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) for the design, conduct, safety, and reporting of clinical trials.

ICH-GCP CHECKLIST FOR CLINICAL STUDY PROTOCOL

- ✓ General Information
- ✓ Background Information
- ✓ Trial Objectives and Purpose
- ✓ Trial Design
- ✓ Selection & Withdrawal of Subjects
- ✓ Treatment of Subjects
- ✓ Assessment of Efficacy
- ✓ Statistics
- ✓ Direct Access to Source data / Documents
- ✓ Quality Control & Quality Assurance
- ✓ Ethics
- ✓ Data Handling & Recordkeeping
- ✓ Financing & Insurance
- ✓ Publication Policy

FINAL REPORT

The final clinical study report should be comprehensive. It should include the data along with an interpretation and discussion of its meaning. It must be written in an understandable manner.