# EVIDENCE-BASED MARKETING WITH CLINICAL TRIAL DATA FOR NUTRACEUTICALS

**Dr. Anish Desai Md. FCP. PGDHEP**
Director, Intellimed Healthcare Solutions

## Introduction

Nutraceuticals industry is following the pharmaceutical industry in several areas including quality, regulations, labelling and packaging. The current trend is towards evidence-based marketing by generating clinical trial data.

Performing clinical trials on finished products presents a clear differentiation of opportunity. Evidence-based recommendations require a technical review of the pertinent clinical literature in which publications are rated according to their level of scientific substantiation.

There is widespread interest in supplements among many stakeholders including consumers, industry members and scientists. Consumer motivations for use of supplements are broad and usually relate to the perceived belief of efficacy involving general well-being, aesthetic pursuits, prevention or management of chronic diseases, longevity, fitness, sports performance, and/or any combination of such factors.

To substantiate, these claims require a varying degree of relevant and credible scientific evidence. In addition to the varying degree of scientific evidence required, there are various regulatory pathways that can be engaged to make a claim on your product depending on its composition.

Nutraceutical trials may be more pragmatic as they document human experiences with specific foods in the context of the human diet while drug trials evaluate the safety and efficacy of a drug in a specific disease. These trials may include both healthy and high-risk people while drug trials include patients with a specific disease needing the treatment. Studies with a strong experimental design help discern between evidence-based findings and those that have not been substantiated. This trend will go a long way in establishing the credibility of nutraceuticals in the minds of the medical fraternity and consumers. However, weak descriptive studies with indirect and correlative measures can lead to misleading conclusions for efficacy.[1]

**Dr. Anish Desai Md. FCP. PGDHEP**

*Director, Intellimed Healthcare Solutions, Honorary Professor Pharmaceutical Medicine , Infectious Disease Department , KEM Hospital, Mumbai, Director Strategic Medical Affairs, Nutragenix Healthcare Pvt.Ltd., Chief - Expert Medical & Scientific Advocacy Board , Expert Nutraceutical Advocacy Council (ENAC)*

*Dr. Anish Desai is a trained Clinical Pharmacologist and Pharmaceutical Physician with 3 decades of experience in Academia, Research, and Healthcare industry with proven leadership skills, strong business acumen, and a deep understanding of the Healthcare System, including Pharmaceutical, Nutraceutical & Medical device industry. He has been recognized for driving positive change, delivering solutions, developing talent and nurturing strong relationships with external stakeholders. Holding Senior Management Position for last 20 years and involved in strategic decision. With an extensive experience in the field of research, Dr. Anish Desai's work is well published & presented in international and Indian peer reviewed Journals and conferences with nearly 150 publications and Abstarcts.*

## Challenges in the Nutraceutical Industry

- Minimal acceptance of the products
- Lack of awareness about the products
- Lack of optimal dose and dosage system
- Lack of formulations other than oral and topical
- Taste
- Cost
- Lack of strong evidence or clinical data
- Lack of data regarding metabolism or other Pharmacokinetic (PK) Data
- The exact mechanism of action is not well established
- Fewer innovations in nutraceuticals compared to pharmaceuticals
- Route of administration is mostly oral (others are less established)
- Proper regulations for nutraceuticals as pharmaceuticals has been lacking

In the era of revolution of natural products, the need of the day is the development of an evidence base for validation of production, evaluation, regulation, safety and allied aspects of natural products. Nutraceuticals are evaluated, validated and regulated in various countries according to their system. We need to understand various evaluation parameters for nutraceuticals to improve quality and increase scientific evidence.

The clinical trials for nutraceuticals are designed to evaluate and substantiate specific marketing claims, while drug trials document the safety and efficacy of a specific drug for a specific indication. Further, nutraceuticals trials may be more pragmatic as they document human experiences with specific foods in the context of the human diet while drug trials evaluate the safety and efficacy of a drug in a specific disease. These trials may include both healthy and high-risk people while drug trials include patients with a specific disease needing the treatment.

## Need for clinical trials

Clinical trials are needed to be conducted in large numbers to generate appropriate clinical data. The safety and tolerability of the product are well known when the trials are done on a larger scale. To gain trust among the general public and medical community, the effectiveness and efficacy of the drug have to be well established. The pharmacodynamics data is clear for nutraceutical products, but it is unclear how the product is eliminated or metabolized inside the body or information about any other pharmacokinetic data. More clinical evidence is needed to be generated to get information about the pharmacokinetics of nutraceuticals by conducting frequent clinical studies. The optimal dose for nutraceuticals is not well established. Most of the dosing is prepared commonly

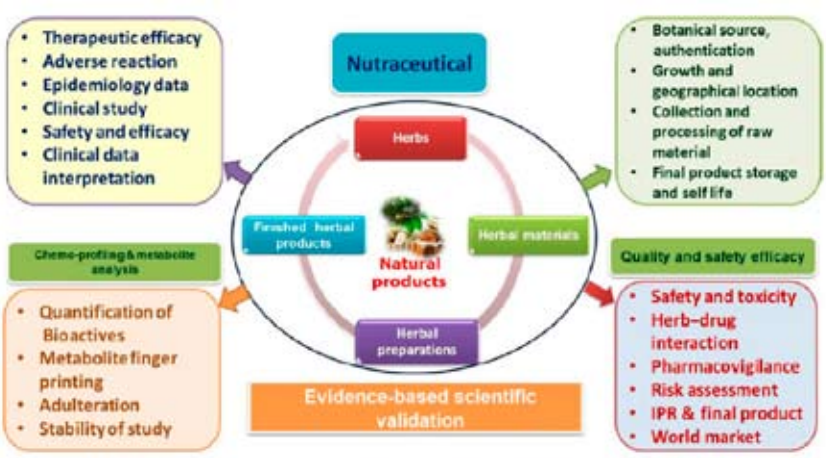


*Figure 1: Evidence-based scientific validation[2]*

for all the disease conditions and populations. Nutraceuticals are mostly found in dosage forms like oral dosages and topical dosages. Due to decreased evidence on the stability and efficacy of other dosage forms, new formulations are not being produced. Marketing is the most reliable way to create awareness among the general public about nutraceuticals, but without sufficient evidence and supporting clinical data it becomes a challenge for marketing nutraceuticals among the population.

## Evidence-based practice

Evidence-based practice is an approach where clinical decisions taken by the health professionals are based on clinical evidence of the drug or product for individual patients. Evidence-based medicine is a mixture of expert opinion, scientific literature, observations and client point of view.

Benefits: There are various benefits of evidence-based practice. Effective patient care can be achieved through evidence-based practice which will eventually improve patient outcomes. EBP gives strong support to individualized treatment regimens. The quality of care provided to the patients by the clinicians is also improved through this approach. EBP helps the healthcare professional to be updated about recent trends and practices.

Challenges: A sudden shift from conventional medicinal practice to evidence-based nutraceutical practice can be a barrier to implementing it. There might be obstacles for new implementation from the management or colleagues.[3] Approval from fellow teammates could be a challenge as there may be more than one health professional in managing a patient. There could be a lack of time to educate about the evidence-based practice to all health professionals. Inadequate access to resources to be used in evidence-based practices can be a challenge to health professionals working in rural areas. Another challenge is the lack of resources to find evidence about the nutraceuticals to support the practice.[4] Difficulties due to lack of teamwork can act as a barrier for nutraceutical evidence-based practice. There could be difficulty in accessing the nutraceutical evidence to support the practice.[3] Lack of time to study or research about the nutraceutical practice can be a challenge.[4]

The principle of evidence-based nutraceutical practice is based on five steps which are:-

1. Preparation of a question that is answerable.
2. Generating clinical evidence for the question.
3. Critical appraisal of the evidence.
4. Application of the evidence.
5. Evaluating the practice of evidence-based medicine.[5]

## Clinical Evidence

Meta-analysis is a statistical analysis where results from multiple scientific works of literature are gathered. Various articles on the same topic are searched from different sources like Pubmed, Cochrane, etc. All the articles are thoroughly studied and a meta-analysis is prepared. Another clinical evidence used is a systematic review which is a review of the evidence for a particular formulated question which is done in a systematic order by identifying, selecting and critically appraising the evidence. A systematic review is considered high-quality evidence for practice.

## Efficacy

Efficacy is defined as the ability of a nutraceutical product/ intervention to show its desired effect/result under certain conditions.[7]

To determine efficacy, there should be certain endpoints/ parameters to be observed such as:

- Clinical Endpoints- E.g.: Decrease in blood pressure, etc.
- Pharmacokinetic Endpoint- E.g.: Serum concentration or half-life of the product.
- Pharmacodynamic Endpoint- E.g.: The nutraceutical product's ability to alter the disease mechanism.
- Laboratory parameter- E.g.: Blood glucose level.
- Harbinger's sign- A warning or sign which indicates underlying condition/ effect.[8]

The study design used to evaluate the efficacy of nutraceuticals are[5]

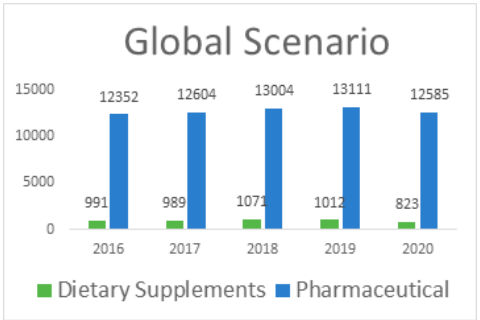


*Image credits: https://clinicaltrials.gov/ (Global: 2016-2020)*

*Figure 2: Global scenario of clinical trials*

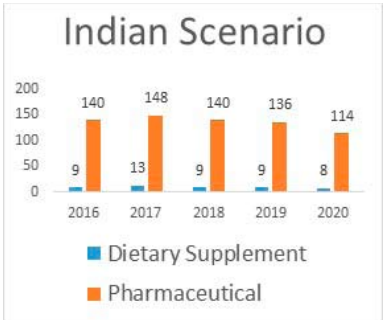


*Image credits: https://clinicaltrials.gov/ (India: 2016-2020)*

*Figure 3: Indian scenario of clinical trials*

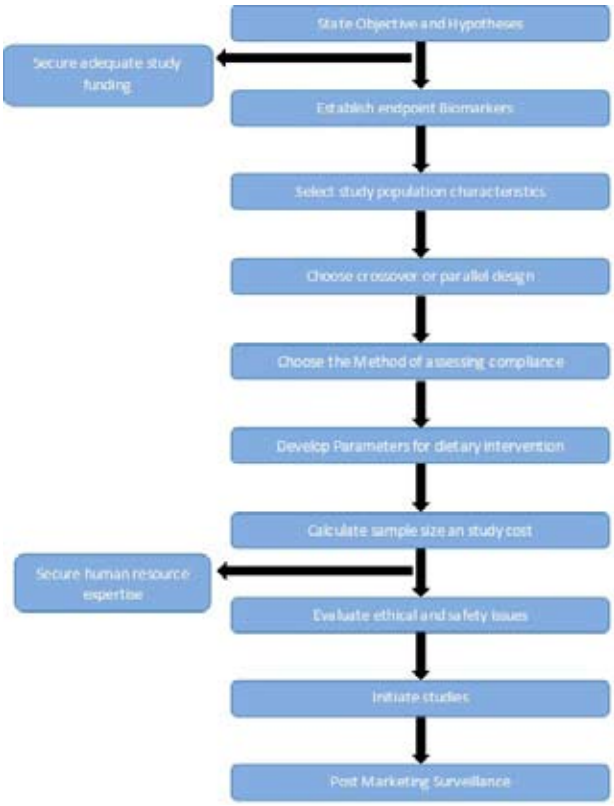


*Figure 4: Stages in designing clinical studies*[6]

i. Observational Studies
   - Cohort studies
   - Case-controlled studies
   - Real-world evidence

ii. Experimental studies
   - Randomized controlled trials
   - Comparative studies (Two-arm trials)

## Patient-Reported Outcomes (PRO)[9]

Defined as a term that covers the health or clinical data reported by the patient regarding a product or studies such as a symptom, adherence to treatment and satisfaction with the therapy. The source for PRO is solely the patient. Following are a few examples of PROs.

- Refractive Error Quality of life survey
- The Medical Outcomes Study 36-item short-form questionnaire (SF-36)
- CLAU-S questionnaire
- Social Phobia Inventory (SPIN) questionnaires applied to screen for phobic disorders

The components for Patient-Reported Outcomes include physical functioning, social functioning, psychological well-being, pain, vital signs, disease-related symptoms, treatment-related symptoms, treatment satisfaction and treatment adherence. These components are considered during assessing a PRO.

## Safety

Nutraceuticals also cause safety issues due to pharmacological alteration and also due to quality issues like misidentification of the plants, adulteration during manufacturing, etc. Pharmacological issues include drug-food interaction, drug-drug interaction and nutraceutical-pharmaceutical interaction.[10] Nutraceuticals have less or no side effects mostly. Side effects like constipation, diarrhoea and vomiting are present. Since nutraceutical preparation lacks proper regulation in comparison to pharmaceuticals, safety concerts are an issue. Pharmacological and toxicological studies of nutraceuticals are complex due to multiple phytochemicals present in one plant (use of fertilizers and pesticides). It is believed that since they are made from natural extracts, there are no considerable side effects. Since there is a chance of contamination of plants with other plants' alkaloids or metals, they may cause slight side effects such as GI disturbances like diarrhoea, vomiting, etc.[11]

Green tea infusion and extracts are used around the world as a beverage, nutraceutical and phytopharmaceutical. Kapetanovic et al. conducted a chronic toxicity study on fasted and non-fasted beagle dogs which are 5-6 months old. They were given modified green tea extract (64%). Dogs are given 0, 200, 500 and 1000 mg/kg/day. The study was terminated at 6.5 months and there were 16 deaths among 24 dogs. The liver lesions were described as centrilobular necrosis and chronic inflammation. Renal lesions were tubular epithelial necrosis, tubular dilation with granular or hyaline protein casts, epithelial regeneration, acute inflammatory exudate and transitional hyperplasia.[12] Side effects of green tea extract in humans are bloating, nausea, heartburn, abdominal pain, dizziness, headache, muscle pain and hepatotoxicity.[13]

Side effects can be caused by other toxic contaminants/adulterants such as phytotoxicants, metals, mycotoxins, pesticides, radiation, drug abuse and therapeutic drugs.[11] The most toxic component present in plant species is Pyrrolizidine Alkaloids (PAs). There are almost 150 PAs that have been identified. Similar toxic effects are seen in most of them, but there is variance in their potency due to their bioactivation in the liver to the toxic metabolites called pyrroles. These pyrroles, which are powerful alkylating agents, react with DNA and protein and cause tissue necrosis and cellular dysfunction.[14] Detection of pyrrolizidine alkaloid in the biological system indicates the use of Comfrey. The target organ for Comfrey is the liver.[15] Nutraceutical specific biomarkers are not available but target organ-specific biomarkers are used to check the toxicity of the nutraceuticals. E.g: SGOT, SGPT and bilirubin for pyrrolizidine alkaloids. Recently, organ-specific microRNAs are useful biomarkers for organ toxicity since this biomarker can show early changes in comparison to other biomarkers.[16]

## Post-marketing surveillance[17]

Post-marketing surveillance is the monitoring of the nutraceutical product in a larger population. The product is distributed on a large scale to check the effect and to investigate the safety concerns in various populations. During this phase, the issues related to the product are noted by the regulatory authority as evidence.

## Conclusion

The nutraceutical industry is gradually emerging and growing in India. Awareness has improved over the years which has led to higher consumption of nutraceutical products. Regulations have

evolved and are now stricter than ever in terms of quality, claims, efficacy and safety. Various challenges need to be resolved to stabilize the growth of the industry. Nutraceuticals, despite being nascent in some therapy areas, their innovation, conducting randomized clinical trials and real-world evidence studies must be encouraged. Although being derived from natural sources, surveillance and safety assessment of nutraceuticals is essential, which is taken care of by 'Nutrivigilance'. Generating more clinical evidence is one of the many primary objectives. Good quality clinical trials, evaluating the efficacy and safety of nutraceuticals in different therapy areas will help in supporting claims, making policies and implementing evidence-based healthcare. By doing all this, the practice of evidence-based nutraceuticals will increase confidence and awareness among healthcare professionals.

## References:


1. http://www.fnbnews.com/Marketing/evidencebased-marketing-with-clinical-trial-data-key-in-nutra-expert-60965
2. Mukherjee, P. K. (2019). Phyto-Pharmaceuticals, Nutraceuticals, and Their Evaluation. Quality Control and Evaluation of Herbal Drugs, 707–722.
3. Newman, M., Papadopoulos, I., & Sigsworth, J. (n.d.). practice. I 998, 231–238.
4. Sadeghi-Bazargani, H., Tabrizi, J. S., & Azami-Aghdash, S. (2014). Barriers to evidence-based medicine: A systematic review. In Journal of Evaluation in Clinical Practice (Vol. 20, Issue 6, pp. 793–802). Blackwell Publishing Ltd. https://doi.org/10.1111/jep.12222
5. Akobeng, A. K. (2005). Principles of evidence-based medicine. Archives of Disease in Childhood, 90(8), 837–840. https://doi.org/10.1136/adc.2005.071761
6. AbuMweis, S. S., Jew, S., & Jones, P. J. H. (2010). Optimizing clinical trial design for assessing the efficacy of functional foods. In Nutrition Reviews (Vol. 68, Issue 8, pp. 485–499). Blackwell Publishing Inc. https://doi.org/10.1111/j.1753-4887.2010.00308.x
7. Bower, P. (2003). Efficacy in evidence-based practice. Clinical Psychology and Psychotherapy, 10(6), 328–336. https://doi.org/10.1002/cpp.380
8. Chin, R., & Lee, B. Y. (2008). Dosing and Intervention. In Principles and Practice of Clinical Trial Medicine (pp. 181–212). Elsevier. https://doi.org/10.1016/b978-0-12-373695-6.00010-7
9. Marquis, P., Arnould, B., Acquadro, C., & Roberts, W. M. (2006). Patient-reported outcomes and health-related quality of life in effectiveness studies: Pros and cons. In Drug Development Research (Vol. 67, Issue 3, pp. 193–201). https://doi.org/10.1002/ddr.20077
10. Bergamin, A., Mantzioris, E., Cross, G., Deo, P., Garg, S., & Hill, A. M. (2019). Nutraceuticals: Reviewing their Role in Chronic Disease Prevention and Management. Pharmaceutical Medicine, 33(4), 291–309. https://doi.org/10.1007/s40290-019-00289-w
11. Gupta, R. C., Srivastava, A., & Lall, R. (2018). Toxicity potential of nutraceuticals. In Methods in Molecular Biology (Vol. 1800, pp. 367–394). Humana Press Inc. https://doi.org/10.1007/978-1-4939-7899-1_18
12. Kapetanovic IM, Crowell JA, Krishnaraj R, Zakharov A, Lindeblad M, Lyubimov A. Exposure and toxicity of green tea polyphenols in fasted and non-fasted dogs. Toxicology. 2009 Jun 16;260(1-3):28-36. doi: 10.1016/j.tox.2009.03.007. Epub 2009 Mar 24. PMID: 19464566; PMCID: PMC2687403.
13. Shimizu M, Shirakami Y, Sakai H, Kubota M, Kochi T, Ideta T, Miyazaki T, Moriwaki H. Chemopreventive potential of green tea catechins in hepatocellular carcinoma. Int J Mol Sci. 2015 Mar 17;16(3):6124-39. doi: 10.3390/ijms16036124. PMID: 25789501; PMCID: PMC4394523.
14. Panter KE, Welch KD, Gardner DR (2014)Poisonous plants: biomarkers for diagnosis. In: Gupta RC (ed) Biomarkers in toxicology. Academic Press/Elsevier, Amsterdam, pp 563–589
15. Hilmas CJ, Fabricant DS (2014) Biomarkers of toxicity for dietary ingredients contained in dietary supplements. In: Gupta RC (ed) Biomarkers in toxicology. Academic Press/Elsevier, Amsterdam, pp 609–627
16. Penman AD, Kaufman GE, Daniels KK (2014) MicroRNA expression as an indicator of tissue toxicity. In: Gupta RC (ed) Biomarkers in toxicology. Academic Press/Elsevier, Amsterdam, pp 1003–1018
17. Lobb, Ano (2009). *Enhancing FDA's Post-Market Surveillance of Dietary Supplements: Two Simple Steps to Build Capacity. Journal of Dietary Supplements, 6(3), 204–210.* doi:10.1080/19390210903149501


## Advertisement Index


| Sr. No. | Company Name | Pg. No. |
|---|---|---|
| 1. | Intellimed Healthcare Solutions | 3,8 |
| 2. | IPA-MSB, ACE | 34 |
| 3. | Elmach Packages (India) Pvt. Ltd. | 22, 23, 44 |