Practical challenges faced in conducting clinical trials for Nutraceuticals and current scenario in US and India

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Abstract: The two phrases that compose the name "Nutraceuticals" are "Nutrition" and "Pharmaceuticals." These are meant to be ingested orally.

Nutrition: Include food or part of food.

Pharmaceuticals: engaged in the manufacture, preparation, dispensing, or sale of drugs.

The concept of nutraceuticals is to put an emphasis on prophylaxis. Hippocrates, a Greek physician, regarded as the father of medicine, said, "Let food be your medicine."

Nutraceuticals led to new era of medicine, and transformed into a research-oriented sector. It includes mainly 1. herbs, 2. nutrients, 3. diet supplements [1]. Types of foods include dietary fibres, prebiotics, probiotics, PUFAS, antioxidants, spices, health drinks, sports drinks, fortified foods, etc. These are often perceived as "safe" and have minimal side effects. Nowadays, it is a popular and attractive type of system used for the prevention of many types of ailments, as the side effects of allopathic medicines are high. But western medicine is dominating the use of nutraceuticals. Nutraceuticals must also have a place alongside novel forms of medicines despite the fact that evaluating them is a difficult problem given the state of scientific knowledge and regulatory affairs.

Role of placebo-controlled double-blind RCT interventional study decentralised study single crossover trial etc and assessment of safety and efficacy as well as risk-benefit analysis it was important to identify and address deceptive elements especially in the context of nutraceuticals to improve the guidelines applicability and relevance to health promotion we must rethink them additionally these point out the drawbacks and complications of conventional RCT and provide proof of concept the purpose and significance of clinical trials for nutraceuticals are explained in the current paper.

Keywords: Nutraceuticals, Dietary supplements, Clinical trial, Evidence Based Nutrition, CDSCO, FDA

Abbreviations: EBN: Evidence-based nutrition; FSSA: Food Safety and Standards Act; DSHEA: Dietary Supplements Health and Education Act; PUFAS: Poly Unsaturated Fatty Acids

Introduction:

The term Nutraceutical was framed by Stephen Defelice. In India nutraceuticals are regulated by FSSA,2006. In USA nutraceuticals are regulated by DSHEA, 1994 and The Federal Food, Drug, and Cosmetic Act (FD&C Act).

Food and nutraceuticals are substantially increasing due to unique health benefits, leading to massive increase in the number of trials for nutraceuticals. Nutraceutical market is very big business in US, accounting billion dollars/year in sales [2]. Products are typically offered in liquid, soft gel, soft capsule powder, oil and powdered form. They work best for preventing or reducing wrinkles, raising physical performance, in bodybuilding, sports, boosting immunity, improving bone health and aiding in the treatment of various disorders. Nutraceuticals are frequently unregulated because they are not recognised as legitimate pharmacological substances like those used in other types of medical systems clinical studies on nutritional supplements are insufficient to make safety claims. This evaluation focuses on obstacles and real-world issues that need to be addressed as well as potential remedies for them.
Companies producing nutraceuticals: In US: Herbal life international, MIRA, Nutra Science Labs, Makers Nutrition etc.
In India: Zoic pharmaceuticals, VATAVE health care, Crius life science group, Bionova life sciences.
Benefits: Natural, reduce health complications, high consumer acceptability, give physiological benefits, increase life expectancy etc.

Nutraceuticals do not often need FDA approval. A producer may still need to do clinical trials even if bringing a nutraceutical product to market may take less time than it does to bring a medication or treatment to market. Before a product can be made available to the general public in some jurisdictions, the maker of a nutraceutical must guarantee that it is risk-free and devoid of contaminants. Manufacturers may also attempt to gain an advantage over rivals by supporting marketing claims with data from science.

Need of nutraceutical clinical trials:
Clinical trials can assist sponsors in fulfilling these standards by demonstrating a nutraceutical's efficacy. A trial evaluates the safety, efficacy, and bioavailability of nutraceuticals [3]. Studies might analyse the effectiveness of a single agent or the overall impact of a product on the consumer. To increase the likelihood that a clinical trial will be successful, preclinical investigations are typically useful in determining the first levels of safety and bioavailability in a product.

The design of trials will change based on the endpoints and biomarkers selected by sponsors. A selected demographic for the nutraceutical trial may include women, athletes, or the elderly. When a clinical trial's goal is to determine a product's effectiveness in the general population, the study requires healthy participants who are both sexes and span a variety of ages. A trial's focus may be on illness recovery, disease modification, or other goals depending on different biomarkers. The ability of dietary supplement tablet or liquid gel capsule, to break down in the stomach and release its contents can also be tested in trials that include a dosage performance assessment.

Trials should also contain a control group to compare the supplement under investigation to a placebo, standard drug or standard of care. Double-blind studies are frequently the best choice.

Evidence-based nutrition (EBN):
Developing dietary recommendations based on clinical experience and scientific data. These are comparable to proof-of-concept tests for traditional medicines. The purpose of drugs is to treat illness. They are not subject to homeostatic regulation by the body and have discrete functions that are intended to target certain organs or tissues. Contrary to most drugs, nutrients target all cells and tissues and have a wide range of effects and outcomes. These have a high level of safety because they are either not bioavailable or are metabolised and/or eliminated quickly.

Clinical studies for medications and dietary supplements varied significantly in terms of subject types, sample sizes, endpoints, surrogate marker identification, informed consent procedures, and other aspects. Most studies on dietary supplements are conducted on healthy volunteers and call for bigger sample sizes to demonstrate their desired effects, which are frequently of lower magnitude when compared to medications.

Dietary supplements frequently contain combinations of ingredients, in contrast to pharmacological clinical trials, where the drug or metabolite(s) are clearly characterised and can be evaluated using standard analytical techniques. The choice of an appropriate biomarker for pharmacokinetic research in people is more challenging and may call for advanced analytical methods. Animal preclinical research can benefit human clinical trials by providing guidance on dosage, dosing schedules, and the most appropriate biomarkers for quantification.

The need for nutraceutical trials significantly increased as a result of unique selling proportions. Clinical trials for nutraceuticals / Nutraceutical clinical trials:
Help the manufacturer by providing advantage over the ever-increasing competition.

Necessary for consumer safety. They act as a gold standard in clinical research. [4]

Problems in nutraceutical trial design:

1. Use of surrogate markers:
A considerable bulk of evidence is required and the trial is ought to last an extended time period if the goal is to say that a product has preventive capabilities. Sponsors may consider using a surrogate marker to state this. The surrogate needs to be suitable, researchers need to trust it, and user have to accept it as a suitable surrogate. For instance, a products surrogate claim can read “reduces levels of bad cholesterol related with more chance of strokes, and heart attacks” rather than “minimize the risk of strokes or heart attacks” [5].

2. Controlled vs uncontrolled trials:
The kind of product, the intended end-point, and financial stipulations are likely to decide whether a trial is controlled or uncontrolled.

Trials should, whenever possible, include a control group. It is best to compare the nutraceutical to a placebo, although regular medical treatment or even a well-known drug could be utilised instead.
Study subjects constantly modify their conduct while individuals are monitored for a trial, making it impossible to verify whether variations detected in people receiving the nutraceutical are attributed to the substance or another cause without a comparative group.

3. Blinded versus open label:

The gold standard is to utilise placebos in double-blinded studies, therefore do so whenever you can. [6]. Blinding is vital when lifestyle choices tend to affect the end-point since subject’s routines will alter if they know that they are taking the active component or not.

In cases where creating a proper placebo is not possible, an open label strategy must be used. This is less ideal because participants in placebo groups are more likely to adhere to the study procedure because they are aware they aren't consuming the active ingredient. Because they have no incentive to continue, study subjects are also more inclined to drop out. Additionally, there are bias issues because participants who know they are taking a placebo are unlikely to notice any improvement in their symptoms.

4. Generable data:

The study and the ensuing findings must be as duplicatable as feasible, and the findings must demonstrate that a nutraceutical may have an impact on a larger population. [7]. The cohort under study must carefully balance being homogeneous enough to see its findings with, but not homogeneous enough to prevent the findings from becoming applicable to wider populations.

By conducting the experiment at various locations, sponsors can better capture a range of environmental and demographic factors, resulting in more accurate results. Clinical trials for dietary supplements are evaluated to see whether the supplement is effective and safe for use in people.

In the case of pharmaceutical products, this evaluation can be taken into consideration, but it is less reliable in the context of nutraceuticals. This is owing to the reality that nutraceutical products still have a number of problems even though they are made using techniques like:

- multiple regression analyses
- central composite orthogonal experimental design (CCOD)

The RCT drug model is neither sensitive to or appropriate for nutritional supplements:

Clinical trials that were double-blinded, randomised, and controlled for placebo were used to evaluate the risks and benefits of medications, but they lacked the sensitivity to document the effectiveness and safety of nutraceuticals. The N-of-1 Level 1 showing is advised as it is more suited for proving the efficacy of nutraceuticals and addresses the shortcomings of the standard RCT in capturing the challenges of these products. The have a number of practical issues, such as interactions, a longer time for absorption, individual variability, and the ability to make a strong causal connection between an intervention and its results. Examples include the ALLHAT study on thiazide diuretics and the anti-diabetic medication tolbutamide, which caused secondary failure of response in patients.

Chlorothalidone was rated as being superior to the current "gold" standard diuretics in the "shaky conclusions" of ALLHAT studies that were covered in EBM. RCT results that were used in treatment were later shown to be unreliable or insufficient for reliance. On the other hand, meta-analyses and systematic reviews are regarded as the new gold standard [8]. The choice of population-based monitoring must take into account any identified individual differences.

The easy success of medications has been built on population-specific approaches and crowd-based medical initiatives like vaccines. Indeed, though RCTs were actually intended to minimise bias in investigation, they have become a point of “conflicting interest.” The intrinsic distinctions among medications and nutrients are the biggest obstacle to the application of RCTs to fields unrelated to drug evaluation, like foods, beverages, and dietary supplements. The purpose of drugs is to treat sickness. They are designed to target particular organs or tissues, have distinct functions, and are not subject to the body's homeostatic regulation. Nutrients target all cells and tissues, in contrast to the majority of medications, and have a wide range of outcomes and effects. This multifunctionality must be taken into account when developing RCTs for nutrients. The reaction to a nutraceutical remedy depends on the body's starting point because many nutrients are homeostatically controlled. Elevated levels for those not subject to homeostatic regulation may be not bioavailable or are metabolised rapidly.

True placebos are not possible:

Nutraceutical research, in contrast, cannot utilise real placebos because the therapies entail consuming nutrients, whose absence may result in disease. When there is no true placebo group and the participants must be "healthy," nutrients have a smaller impact size and a longer reaction time to detect health effects. Given that essential nutrients are necessary for health, the fundamental hypothesis that low or inadequate nutrient intake either directly causes disease or worsens it is supported. Heaney asserts that "with nutrients, the question is never 'whether,' but rather 'how much?'" Therefore, EBN is a complex and difficult puzzle. Only one nutrient function—the first to show up and result in illness or death—is used in the definition of a disease (i.e., deficient syndromes like beriberi and scurvy). The problem in showing the numerous advantages of a single nutrient, however, when the evidence of efficacy is constrained to EBM, derives from our awareness of all the other roles (beyond inadequacy).
Endpoints should be global and multifunctional:
Multifunctional effects could be applied to an intricate measure that is typically disregarded in the light of solely one primary result. Due to the increased likelihood of false negative findings, the measure would be deemed useless. The multifunctional result hypothesis of nutrients in the human body correlates to a global outcome that assesses and ranks the impacts of an experimental product across systems, which is a more accurate statement.

Following are to be kept in mind while conducting a clinical trial:
1. Study description: Disease and drug used
2. Study design: Study Type, Actual Enrolment (number of participants), Observational Model, Time Perspective, Official Title, Actual Study Start Date, Actual Primary Completion Date, Actual Study Completion Date
3. Study population: placebo, controlled, diseased etc.,
4. Inclusion exclusion criteria/eligibility criteria
5. Outcome measure
6. Study Protocol design
7. Sample Size Calculation
8. Study Database / electronic case report form (eCRF) Design
9. Identification of Primary and secondary data points that are ideal for statistical calculations
10. End-to-end Clinical Trial Management
11. Subject Recruitment and Retention strategies
12. Study Data Management
13. Clinical Data Statistical Analysis
14. Preparation and Submission of Final Clinical Study Reports

Challenges:
- Businesses in the industry don't understand clinical trials
- It is feasible to derive/borrow information and claims from previous investigation if a product's active components or makeup are the same as those employed in prior trials.
- Less motivation exists since a component may already be the subject of more extensive claims. [9]
- Deciding on an endpoint and determining the claims that companies wish to generate in a nutraceutical study are difficult tasks. Prior beginning a comprehensive study, sponsors should select the allegations for against which they wish to gather evidence.
- Food and ingredient producers frequently have little or no budget set out for trials (budgetary/financial problems).
- Statistical analyses need to be refocused.
- Another significant issue is adulteration of goods.
- The concept's proof is lacking because there aren't enough clinical trial data.
- Nutraceutical complications brought on by toxin contamination may result in mistakes.
- Trials employing nutraceuticals often encounter greater rate of discontinuation versus those using pharmaceuticals therefore are challenging to recruit for. (9). This is because participants in nutraceutical studies are generally held to greater standards than those in pharmaceutical trials since they are expected to lead healthy lifestyles and collect more important data, both of which are difficult to achieve.
- To conduct a relevant investigation, a sample size broader than what is essential in a pharmaceutical trial is frequently required. Consequently, bigger budgets are needed.
- Determining the claims that sponsors wish to make in light of the trial's results is likewise fairly difficult. As a result, to learn more about the expected results, a pilot study may be necessary. Increased costs are the effect of this once more. Sponsors must choose which claim they want to substantiate with evidence before beginning a full trial.

Steps to overcome the challenges:
It might be complicated to select endpoints and biomarkers for research as there are so many potential advantages associated with a nutraceutical product. A clinical investigation must also have a trustworthy biomarker for the relevant biological outcome in order to be productive. As a result, these clinical investigations frequently require pilot research to learn more about the targeted outcomes, which doubles the expense and time required. Although dietary supplements and other nutraceuticals contain natural ingredients that can be found in everyday foods, clinical studies that are used to evaluate them must adhere to strict design criteria. A trial must first implement quality control to guarantee that every batch of the product being evaluated includes an equal amount of active chemicals. Additionally, dietary supplement research investigations need more participants than drug trials while still achieving the lowest standard deviation possible. It can be challenging to find study participants since they must maintain a healthy lifestyle and take part in numerous monitoring tasks in order to collect relevant data. Since lifestyle decisions have a greater impact on the effectiveness of nutraceuticals, they should also be taken into consideration. This is due to the fact that the health effects of nutraceuticals are frequently insignificant in comparison to those of medications and are easily influenced by environmental factors. The problems in recruiting are frequently made worse by these stringent standards.
Studies employing nutraceuticals may also have larger rates compared to research employing pharmaceuticals. Participants may be asked to meet more demanding requirements, such as upholding a healthy lifestyle or recording more data in order to collect large amounts of data. This may make it harder to keep patients. All of these difficulties can be eliminated though, with appropriate trial supervision and design. The success in the medicine and nutraceutical businesses is due to tried-and-true tactics that clinical research organisations (CROs) employ.

**Regulatory framework comparison between India and USA:**

<table>
<thead>
<tr>
<th>Regulation for licensing and registration</th>
<th>USA</th>
<th>INDIA</th>
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<tbody>
<tr>
<td>By United States Food, and Drug Administration (USFDA), Office of Dietary Supplements (ODS)</td>
<td>By Food Safety and Standard Authority of India (FSSAI)</td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>USFDA defines Nutraceuticals as “Dietary Supplements” Under DSHEA</td>
<td>FSSAI defines Nutraceuticals as “Foods for special dietary uses”</td>
</tr>
<tr>
<td>Act/Regulatory authority for registration of nutraceuticals</td>
<td>Dietary Safety and Health Education Act</td>
<td>Food Safety and Standard Authority of India</td>
</tr>
<tr>
<td>Regulations w.e.f</td>
<td>1994</td>
<td>2011</td>
</tr>
<tr>
<td>Regulatory requirements for registration</td>
<td>Product licensing, evidence requirements for safety &amp; efficacy, labelling, health claims, GMP, adverse reaction reporting and clinical trials [10]</td>
<td>Product evaluations, licenses, health and label claims</td>
</tr>
<tr>
<td>Form for registration</td>
<td>Form 3537</td>
<td>Form A, B. and C</td>
</tr>
</tbody>
</table>

**Statistical evidence from last 5 years:**

<table>
<thead>
<tr>
<th>Year</th>
<th>US</th>
<th>India</th>
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<tbody>
<tr>
<td>2019</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>2020</td>
<td>20</td>
<td>9</td>
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<td>2023</td>
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As per the last 5 years the nutraceutical clinical trials in US and India were displayed in the above diagram. In 2019-6 trials; in 2020-8 trials; in 2021-14 trials; in 2022-33 trials; in 2023-15 trials and previous years-41 trials were conducted in US. Out of 117 total trials, 61 trials were completed and remaining were under process. [11]

Likewise, in India, 2019-20, 2020-25, 2021-20, 2022-24, 2023-9 trials were conducted. Out of total 118 trials, 40 trials were completed and remaining were under process. [12]

**CASE STUDY:**
The combination of meal replacement, fish oil, and calorie restriction resulted in "productive weight management" and enhancements in metabolic syndrome in trial subjects. According to the findings, participants dropped an average of 4.5 kg of weight, 6.5 cm of diameter at the waist, and 2.5% less body fat throughout the course of the 12-week experiment. This method also had an effect on the levels of triglycerides, lower density lipoprotein cholesterol (LDLc), and fasting blood glucose.

**Clinically Beneficial Fish Oil in the Management of Metabolic Syndrome in Combination with Calorie Restricted Diet and Meal Replacement:**[13]

In Taiwan, 188 patients with metabolic syndrome volunteered for this clinical study. They were placed into each of the four groups by chance and observed for 12 weeks while on a "calorie restricted diet,” "calorie restricted diet with meal replacement,” "calorie restricted diet with fish oil,” or “calorie restricted diet with meal replacement and fish oil.” 179 people finished the trial satisfactorily.
RESULTS:
As stated in the study's conclusions, on average, participants in the "calorie restricted diet with fish oil" group lost 4.5 kg of body weight, 6.5 cm of waist circumference, and 2.5% of their body fat. Likewise, it was observed that when compared to each of the three groups, the "calorie restricted diet with meal replacement and fish oil" group also saw improvements and stability in fasting blood glucose, triglycerides, LDLc, blood pressure, and the overall metabolic syndrome.

Twenty to thirty percent of adolescents globally have metabolic syndrome. It can be recognised by spikes in blood pressure, cholesterol, fasting blood sugar, and waist circumference. Metabolic syndrome increases the risk of both heart disease and diabetes.

Discussion: Nutritional imbalance was brought on by changes in eating habits that significantly altered lifestyle. By supplying enough nutrients, or in the case of health promotion and illness prevention, nutraceuticals are used to help maintain the balance. It's crucial to focus on elements linked to quality, safety, and efficacy. The use may result in a number of interactions that could be deadly or synergistic. Regulatory authorities will benefit from increased precision and accuracy of nutrient measurements, bioactive marker molecules for other components, natural toxins, hazardous substances, and/or pesticides in dietary supplement ingredients and final products. Therefore, clinical studies must be carried out in order to identify some of the common interactions, to get the right results, and to try to minimise the risks. Although they are a component of food, nutraceuticals are not given special attention. All regulatory agencies are concentrating on the success of the experiments so as to safeguard the wellbeing of users. Clinical trials are undertaken for practically all nutraceuticals in the USA, while there are few in India.

Conclusion: This article emphasises the need for clinical trials for nutraceuticals and the difficulties encountered during these investigations because they are the foods of the future. Nutraceuticals make up a prospectively expanding sector that work in the fields of nutrition and medical disciplines providing comprehensive medical care. However, among other issues, contemporary trends in nutraceutical research are neither adequate nor necessarily satisfactory for the modern lifestyle. The goal of this paper is to list the difficulties and offer suggested solutions to the problems that emerged during the nutraceutical studies.

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