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An assessment of clinical trials used in functional food science

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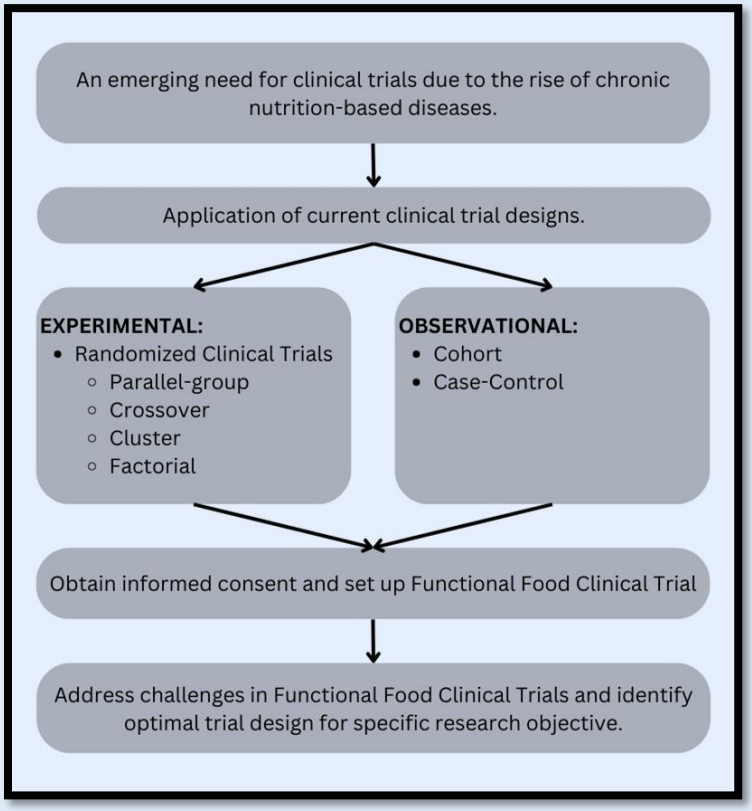
ABSTRACT: The emergence of chronic diseases with nutritional origin has rendered the wide use of clinical trials and intervention strategies necessary. Clinical trials have become a "gold standard" for testing the health impacts of different dietary changes; however, they also pose a potential risk to participants. Particularly with clinical trials used in food studies, there is an added complexity of food chemistry and food behavior as well as unique ethical issues related to clinical nutrition trials such as a potential violation of the right to be fed, disruption of food culture, and the need for food security. Thus, it becomes imperative to have a basic understanding of the key principles and methodology of different clinical trials to enable researchers to determine the best type of clinical trial for their functional food nutrition study. The progression of clinical nutrition trials is promising, but there is an increased importance of reviewing different models to determine the best method of performing nutrition-based research that minimizes the potential risk to participants while increasing current food knowledge. In this article, we aim to achieve two major goals: the first is analyzing various types of clinical trials and the second is using this analysis to figure out which type of clinical trial is ideally suited for research related to food and nutrition.

Conclusion: We conclude that randomized trials are the most effective type of clinical trial used in functional food studies. Randomized cluster trials and randomized parallel-group trials are particularly effective in diminishing the challenges in functional food studies that are outlined in this paper as they reduce the effects one intervention has on another intervention.

KEYWORDS: Clinical trials, Functional Food Science, Clinical research, Functional Food, Food, Nutrition



INTRODUCTION The use of clinical nutrition trials is imperative in reducing the prevalence of chronic disease due to food pathogenicity. Varying nutritional causes and nutrition-based causes have been linked to health problems. However, it is no secret that there are varying complexities associated with clinical nutrition trials and challenges associated with the human relationship with food that differ largely from pharmaceutical clinical trials or other health-related trials [1]. These complexities have questioned the use of clinical trials as the "gold standard" in nutrition research and have highlighted the importance of evaluating various models to determine the ideal type of clinical studies that can be used in nutrition-based research [2].

Clinical trials are a type of study that involves people for the purpose of clinical research studies. While observational studies include the gathering of information about people in normal settings through observations, clinical trials are research studies performed on people with the aim of evaluating a medical or behavioral intervention and are typically used to test the efficacy of a new treatment compared with a standard treatment. Clinical trials used in functional food science can sometimes be more complex than clinical trials used in other medical studies due to the complexities that come with food chemistry and food behavioral changes. However, a rapidly changing food supply and the need to expand on food health have made

the use of clinical trials in functional food science more prominent [3].

The aim of this study is to evaluate different types of clinical studies used in functional food science and determine which type of study is best suited for functional food trials based on the common challenges present in functional food trials.

***OBSERVATIONAL STUDY – COHORT STUDIES*:** Cohort studies are useful for examining associations, generating hypotheses and can study multiple endpoints and examine temporal relationships. However, they also tend to be time-consuming, require a large sample size and many resources, are mostly effective only for common diseases, are expensive, and susceptible to confounding variables [4].

Cohort studies are particularly useful in evaluating the occurrence of a disease in a particular set of people and are frequently used in outbreak investigations to determine the source of an outbreak [4].

OBSERVATIONAL STUDY – CASE-CONTROL STUDIES: Unlike cohort studies, case-control studies begin with a sample experiencing a disease which is then compared with a control group that is not experiencing the illness being investigated.

Both cohort studies and case-control studies are beneficial for examining associations and generating hypotheses and are typically quick, easy, relatively inexpensive, and useful in evaluating rare diseases. However, case-control studies only measure relative risk, are restricted in their measurements, have an unclear temporal relationship, may be impacted by confounding variables, and are subject to recall and survivor bias [5].

EXPERIMENTAL STUDY – RANDOMIZED TRIALS: Randomized trials are useful for examining causation and testing hypotheses. Randomized trials have long been considered the “gold standard” for evaluating treatment intervention and are useful as they allow for extensive control over the research process and are not susceptible to the influence of confounding variables. However, randomized trials are also time consuming, expensive, limited in generalizability, and it is more common to see dropouts in randomized trials [6].

Randomized trials have been largely overshadowed by epidemiology and observational analyses in nutrition research. Typically, nonrandomized observational studies are favored over randomized trials due to the potential for crossover, cross-in, withdrawals, and poor adherence that comes with people changing their choices. However, these are examples of why randomized trials are preferable and irreplaceable compared to epidemiologic studies, especially because randomized trials allow for well-controlled experiments that are needed to study mechanisms and acute-change physiology [7].

The randomized controlled trial is a comparison of the action of the experimental treatment versus the untreated group. The comparison of the two groups occurs under strictly controlled conditions to increase the chances of yielding generalizable results. It is important to note that clinical trials may be impacted by potential confounding variables, but this risk is diminished with the use of randomization.

There are several ethical issues regarding the use of clinical trials, mainly stemming from the fact that those who participate in nutritional clinical trials are different from the people who gain from the clinical trial. Participation in clinical trials leads to a risk due to potential exposure to unexpected side effects of a new treatment. This issue is amplified because trials are not designed to treat trial participants but rather to create generalizable results.

Randomized clinical trials can also be tested for superiority, non-inferiority, and equivalence. These trials can further be divided into different types:

1. Cluster trial: Pre-existing groups of people are randomly assigned to either the intervention or placebo.
2. Parallel-group trial: Participants are randomly assigned to either the placebo or the intervention.
3. Crossover trial: Participants are randomly assigned to receive either the intervention and then the placebo or vice versa.
4. Factorial trial: Participants are randomly assigned to receive a combination of placebos and interventions.

Cluster Randomized Controlled Trials: There are various types of randomized trials, one of which is cluster randomized controlled trials, also known as group randomized trials or community-randomized trials. These are multilevel experiments where observational units are grouped individuals that are randomly assigned to experimental conditions and outcomes are recorded at the individual level. Cluster randomized controlled trials are similar to parallel-group trials in that participants are randomly assigned to either the intervention or the placebo in a study. These types of trials are beneficial in that they prioritize the randomization of a treatment over the randomization of an individual which reduces the risk of confounding variables impacting the results of the study. However, cluster randomized controlled trials differ in that groups of individuals are randomized, rather than individuals. Unfortunately, errors are common in cluster randomized controlled trials, likely due to investigator confusion regarding how the unit of randomization affects causal inferences and the statistical procedures required for the valid estimation and testing of effects [9-10].

One of the first steps to doing research is choosing a suitable study design from two main categories: observational and interventional studies. Observational study designs are also known as epidemiological study designs and are often used to assess potential causation in exposure-outcome relationships. These study designs also influence preventive methods and include diagnostic study designs such as diagnostic accuracy designs, diagnostic cohort designs, and diagnostic randomized controlled trials. Another type of study design is interventional studies which are often prospective and focus on evaluating the direct impacts of treatment or preventative measures on a disease. Both study designs have significant advantages and drawbacks, and it is important to select which one to use based on the research objective [11, 9]. In functional food studies, a food's function is evaluated based on its impact on the health of those who consume said food. Intervention studies, therefore, are ideally suited for functional food trials as they concentrate on evaluating the effect of a treatment on an individual or a group of people. Cluster randomized controlled trials in particular may be best for functional food studies as they reduce one of the challenges experienced in functional food studies: the effects of confounding variables impacting the results of the study. Additionally, cluster randomized controlled trials tend to cost less money and allows for interventions to be studied without the influence of individuals' decisions.

Parallel-group trial: Parallel-group trials are the most common type of clinical trial utilized in study design. In parallel-group trials, subjects are randomly assigned to one or more study "arms" and each study "arm" will be assigned to a different intervention. Typically, participants will be randomly assigned to either an intervention or a placebo and therefore there is a reduced possibility of the effects of an intervention carrying over to another intervention. Additionally, there is a smaller dropout rate and parallel-group trials typically do not require too much time. However, parallel-group trials typically require a greater number of study participants

and there is a greater possibility of con-founding variables impacting the results of the study as compared to other types of randomized trials such as crossover trials [8].

Crossover trials: Crossover trials reduce the risk of participants being harmed by a placebo. In crossover trials, participants receive multiple interventions, and the effect of different interventions are measured on the same individuals. This benefits the researcher as there is a reduced effect of confounding variables as all the interventions are measured on the same participants and participants can serve as both the control group and the treatment group, therefore, fewer study participants are required. However, crossover trials are best conducted for chronic diseases as they can only be used for diseases that persist for a long time. Additionally, as crossover trials include providing multiple interventions to participants, there is a risk of the effects of one inter-vention carrying over to another treatment and this leads to a greater probability of a Type II statistical error (falsely accepting the null hypothesis that there is no association between variables) occurring [9].

Factorial Trials: Typically, randomized controlled trials involve one to two intervention groups. However, about a quarter of randomized controlled trials in published scientific literature randomize participants to three or more treatment groups. These studies are referred to as "multi-arm" trials as they randomize participants to three or more treatment groups. One example of multi-arm trials is factorial trials which are designed to achieve "two trials for the price of one". This is based on the condition that the effects of the different intervention strategies are independent. Therefore, the treatments selected for factorial trials should not have any known clinical interactions and ideally different mechanisms of action. If these conditions are met, factorial trials may be the best available way to investigate interactions between treatments [9, 12].

Use of a Placebo: In clinical trials, a placebo may also pose a risk to trial participants. This is because placebo-controlled trials require the use of deception as patients who are receiving the placebo may be made to believe that they are receiving a working treatment, which is a deceptive tactic inherent to these types of trials as participants are told that they will not know whether they are receiving active medication or a placebo [4].

The use of a placebo may also pose a potentially harmful risk to participants due to the lack of an active treatment in the placebo. This is particularly relevant to pharmaceutical studies because the absence of an active ingredient in a drug that is being tested may lead to higher levels of pain, more health complications, and potentially even death. One way to avoid the harmful effects of placebo-controlled trials is by using the same population of participants for the placebo and the active drug so that all participants receive treatment. This is commonly referred to as a crossover trial, which is used in pharmaceutical trials and functional food trials to eliminate the issue of potential side effects of ingesting a product that is missing the active ingredient, but crossover trials can diminish the efficacy of the clinical trial by increasing the duration of the clinical trial which leads to increased costs and decreased participant compliance, and creates the additional challenge of creating a placebo that has a similar texture and taste as the functional food that is being tested.

Informed Consent in Clinical Trials: Clinical trials require the use of informed consent which is defined as "a procedure through which a competent subject, after having received and understood all the research-related information, can voluntarily provide his or her willingness to participate in a clinical trial" [19]. Researchers can legally proceed without informed consent when it is unrealistic to gain consent and research provides important clinical relevance. However, whenever possible, adequate disclosure about the research and voluntary declaration of consent is critical [13]. The

criteria needed to obtain ethically valid consent from study participants includes providing information regarding the research, health conditions required for the research project, expected duration of the subject's participation, any risks or benefits associated with the research, a description of the study treatment or intervention, details about the handling of treatment results, protection/confidentiality/privacy details, and any other information deemed necessary to help the subject make an informed decision.

Informed consent is a critical part of the approval process of clinical trials. Research Ethics Committees evaluate trial protocols and assess the trial protocol based on a set of standards. During the trial, researchers cannot change the protocol without informing the committee ahead of time [14].

Setting up Functional Foods Clinical Trials: Trials must be long enough to maintain biological efficacy based on the specific dose, frequency, and timing of active food ingredients. Regulatory authorities recommend at least 3 weeks for intervention studies [15]. For example, the United States (US) Food and Drug Administration (FDA) suggested that studies involving the effect of saturated fats on serum low-density lipoprotein cholesterol concentrations should last at least 3 weeks [16]. Health Canada has also published guidelines on clinical trials involving dietary fiber products and has recommended a 3-week observation period for studying the effect of dietary fibers on lipid metabolism and has recommended a 6-week observation period for studying the effect of dietary fiber on weight control [17]. Many functional food related studies, however, last for approximately 12 weeks, or 84 days, which is typically considered the standard for the Functional Food Center [18-22]. Therefore, it is recommended to have studies last about 12 weeks to yield the desired biological effect without compromising the time, expense, and compliance of trial subjects. This complies with an approval system of the health function of different foods in Japan known as FOSHU [18-22]. Prolonged periods of intervention that last for several months oftentimes lead to higher costs, a reduction of subject compliance, and other logistical issues

Challenges in Functional Foods Clinical Trials: As functional foods clinical trials are becoming more popular; it is important to understand the challenges that come with using functional foods as intervention strategies [23]. While many challenges continue to be faced by functional foods clinical trial researchers, some possible solutions do exist, as discussed in Table 1.

The first challenge to functional food clinical trials is the lack of financial support from industrial funders. In drug-based clinical trials, the sponsor is usually the industry. Pharmaceutical companies typically fund a trial to advance knowledge on a new drug when there is a potential opportunity for commercialization and patenting protection. Functional foods do not usually have a significant gain that justifies a large financial investment, nor are there patenting protections in most functional food products [24].

The second challenge to functional food clinical trials is a lack of technical knowledge to support the trial. Large pharmaceutical companies usually have employees fluent in Clinical Trial Applications (CTA) and ethics proposals documents which are not commonly found in the field of functional food [24].

The third challenge to functional food clinical trials is the lack of a potential placebo. Placebos are an essential control of clinical studies. In pharmaceutical trials, often the placebo is the drug that is being tested without the active ingredient. However, it is harder to find a suitable placebo in functional food clinical trials as food placebos may lack the same texture, taste, and appearance as the food being tested [24-25].

The fourth challenge to functional food clinical trials is the difficulty of delivering food to patients. In pharmaceutical studies, patients will get the tested drug at a physician's office. However, in functional food clinical

trials, it is difficult to regularly deliver food to patients [24, 26-27].

The fifth challenge to functional food clinical trials is that food quality diminishes quickly and with low quality flavor, texture, and taste, trial compliance will diminish. Food that is used must be fresh and have various choices in flavors and tastes. Clinical trials should be short to ensure subject compliance and be cost effective while also being long enough to ensure biological efficacy. Therefore, functional foods should be selected based on dose, frequency, and diurnal timing and these criteria should be used when designing a high-quality clinical trial that meets the study objectives.

One possible solution is delivering foods in a frozen state during regular intervals after being prepared and flash frozen [26]. However, this is conditional on patients owning a freezer and therefore may be a challenge for studies involving economically disadvantaged populations. It is also useful to carry out preliminary smaller trials that allow for food to be eaten in a timely manner and ensure that bioactive compounds contribute to the desired biological effect [24].

The sixth challenge is providing food that is accepted by the patients in the trial. Food must be tasty to ensure patient compliance in the functional food clinical trial. This is not as much of an issue in pharmaceutical studies but requires collaborative time and expertise from the food industry in functional food clinical trials [24].

The seventh challenge is the difficulty of maintaining patient compliance as it is easy for patients to access food. Many foods that are used in functional food clinical trials are available to patients at stores and are very easily accessible which makes it more difficult to control what happens during the clinical trial. This differs from pharmaceutical trials where it is much more difficult for patients to access the drug that is being tested outside of the clinical trial [25].

Moreover, there may be difficulty maintaining patient compliance as patients may share food with family members. This makes it necessary to enforce the rule that patients only consume the functional food product in the presence of the investigators, however, this may be even more difficult as it requires patients to travel to where the functional food product is and is therefore impractical for long-term studies [25].

Another challenge to functional food clinical trials is the difficulty in finding plasma biomarkers that are unique to the functional food being studied. Plasma biomarkers are particularly important in functional food clinical trials in order to determine patient compliance. However, the plasma biomarkers must be unique to the functional food. The bioactive compounds within the functional food must be unique to avoid being confounded with any foods that contain the same compounds [26, 40]. Biomarkers are biochemical changes that can be recognized by various technologies. For example, in a FlaxPAD trial, alpha-linolenic acid and two enterolignans derived from flax were used as plasma biomarkers. Having multiple biomarkers provides more confidence in patient compliance.

Like the seventh challenge of ease of access to the functional food product, members of the control group may inadvertently consume the functional food product. This is because the functional food product may be readily available in stores [26, 34].

The next challenge to functional food clinical trials is designing the study and interpreting the statistical results [1]. In pharmaceutical trials, a statistician is a key part of the study but oftentimes in functional food trials, they are brought in too late in the trial which impacts the data analyses [26, 29].

The final challenges are the responses from the public and the medical community. The public generally understands functional food clinical trials better than pharmaceutical trials. However, most of the information regarding functional foods comes indirectly from the media and from physicians [30, 31]. As the information is delivered indirectly, this may lead to a lack of transparency of the functional food clinical trial to the public.

On the contrary, the medical community may also distrust functional food clinical trials as there is generally some distrust of data from the scientific community due to the idea that there has been inadequate peer review of published results in functional food science or other natural health products due to poor controls, small sample sizes, and less than optimal trial designs [16, 26]. Using mechanistic data and multi-site trials may alleviate potential negative responses from the medical community regarding functional food clinical trials.

Table 1: The challenges of functional food trials and possible solutions to resolve the challenges faced by functional food trial researchers.

Challenges of Functional Food Trial	Possible Solution(s)
1. It is more difficult to acquire adequate industrial funding to support functional food trials	Use competitive grant support, Funding through federal agricultural institutions, Persistent discussions with possible industry sponsors, University-industry partnerships, and Encouraging governments to consider innovative funding options from other countries [23]
2. Lack of technical knowledge to support the trial	Acquire local expertise to fill out CTA and ethics proposal documents prior to starting the clinical trial. If local expertise is not available, source national or international expertise in the area [23].
3. The placebo may not be appropriate	Use of food panel testing prior to using the foods used in the trial may produce an appropriate placebo food and then surveying patients on whether they know which group (control or placebo) they were in [30-31].
4. Difficulty delivering food to patients	No solution
5. Food quality diminishes quickly	Use a variety of foods that contain experimental ingredients [23].
6. Taste may impact the acceptance of food	Maintain close interactions with local industry partners
7. It is easier for patients to access food so people may inadvertently consume restricted foods	Provide a clear indication of which foods are allowed and which foods are restricted to patients and rely on patients to maintain compliance with the study, use a reliable biomarker to ensure compliance of patients is maintained.
8. Possible lack of compliance because patients can share food	Provide a clear indication for the food dosage required by the clinical trial and rely on patients to maintain compliance with the instructions, use a reliable biomarker to ensure compliance of patients is maintained.
9. Using plasma biomarkers unique to the functional food being studied	Use of multiple biomarkers that may be unique to the specific functional food being studied
10. Possibility of patients in the control group inadvertently consuming the functional food being studied	Use of a double-blind study and detailed knowledge regarding the foods being tested given to both groups of patients, Use of multiple biomarkers to ensure patients did not inadvertently consume the functional food they were not supposed to consume.
11. Taking too long in the clinical trial to employ a statistician [28]	No solution
12. Potential negative responses from the public	Be transparent about all processes taking place during the clinical trial, Avoid conflict of interest situations, Keep expectations of the public at a reasonable level
13. Potential negative responses from the medical community	Use of mechanistic data, Confirm initial trial results, multi-site trials

The Past vs. The Future: Functional food clinical trials and the use of nutrition clinical trials, in general, are relatively modern and have progressed from small observational studies to small comparative trials to now larger clinical trials facilitated by more advanced use of statistical concepts and methodological design. Clinical nutrition research has a promising future as trials with larger sample sizes are being conducted and facilitated by better methodology, transparent reporting, and greater use of networking as is seen in Table 2 [12].

Table 2: A comparison of nutritional clinical trials in the past, present, and future.

	Past	Present	Future
Study Methodology	Small, physiological, observational studies, often with underdeveloped protocols [31-34, 37-38]	Larger trials that are much larger, more well-developed protocols [31-32, 48]	Larger sample sizes, adaptive trial designs
Population	Specific populations from specialist centers	General, heterogeneous populations [42-43]	Homogenous populations based on anticipated response to nutritional intervention
Intervention	Specific, comparison-based interventions	More general interventions [39- 41]	Patient-specific, based on specific mechanisms
Outcomes	Specific outcomes based on specific interventions [45-46]	Strong clinical outcomes such as mortality	Patient recovery, functional outcomes

Early nutrition trials were mostly observational and focused on measurements of physiology and patho-physiology based on patients' clinical progress. Past nutritional trials were typically smaller in size and did not always employ optimal techniques such as rando-mization, blinding, and allocation concealment. Statistical methods were relatively underdeveloped compared to present clinical trials partly due to a lack of understanding of study methodology. Early trials also targeted specific populations and frequently utilized convenience samples which may have led to bias in the results. Interventional trials were also driven mainly by industry needs, rather than initiated by investigators. Typically, early nutrition trials were not linked to clinical outcomes and instead focused on short-term physiologic outcomes, and later nutritional trials focused on clinical outcomes but could not always identify the source of a health issue that was being investigated [13].

At the present, nutritional trials typically consist of larger sample sizes, better use of statistical methods such as randomization and blinding, and better planning and organization of the trials themselves. Compared to past functional food clinical trials, larger trials are being used in nutritional studies more often and target hetero-geneous critically ill populations with the objective of improving critical care nutrition. However, short-term nutrition interventions are being commonly studied which calls into question the ability to generalize the results from these studies. The outcomes of present-day nutritional trials are clinically focused that are objective and equally valued by researchers, clinicians, and patients.

Nutritional clinical trials are rapidly evolving and are on track to becoming more patient-specific and based on specific mechanisms and individualized treatments. Larger randomized trials are expected to be used more frequently but should be preceded by preliminary research and more adaptive trial designs [47- 49]. Nutritional clinical trials are also expected to focus on homogenous populations based on the anticipated

response to a nutritional intervention and will likely be much more patient-specific [50-53].

Functional foods were introduced in 1984 as a way of combating rising healthcare costs and continues to evolve today [54-55]. Japan developed Foods for Specified Health Uses (FOSHU) to serve as a standard for functional food products [54]. However, it is necessary to recognize functional food science as a rapidly developing field. Functional food science differs from food science in that it concentrates on food with added bioactive compounds which improve health and prevent disease [55]. The definition of functional food is also constantly changing but the Functional Food Center (FFC) currently defines functional food as "**Natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms**." [56] Bioactive compounds refers to the chemicals found within functional food products that promote health and combat disease under certain conditions [57]. For example, squalene is a bioactive compound that has been of particular interest to scientists due to its anti-inflammatory properties [58]. In addition to providing a definition, the FFC has proposed a methodology for the development of functional food products that involves determining the relevant bioactive compounds in food, providing preclinical studies on efficacy and safety followed by clinical trials on dosage, efficacy, and safety, educating the general public, and more [59].

CONCLUSION

Clinical trials in nutrition are rapidly evolving to larger, more individualized, and more clinically relevant trials. There are various types of clinical trials utilized in nutrition research and researchers should consider their research objectives and goals for their project to determine which type of clinical trial to use. Nutritional clinical trials continue to face various challenges but there are several ways to solve the issues that are experienced during clinical trials.

Different clinical trials can be used in functional food trials depending on the objectives of the study. Randomized controlled trials, despite being relatively expensive and requiring an extensive period of time, are particularly useful in determining a causal relationship and eliminating potential confounding variables through randomization, and therefore are a popular choice in functional food clinical trials.

Despite the challenges associated with functional food trials compared to pharmaceutical trials, the use of functional foods is becoming increasingly popular in the management of chronic diseases and in promoting human health and well-being.

The definition of "functional food" is continuously evolving and the role of functional food in the pathogenesis of chronic diseases needs to be thoroughly studied. Despite the importance of functional food clinical trials, there remains a certain amount of skepticism among both the public and the medical community as well as other challenges that need to be overcome during functional food clinical trials.

Crossover trials and factorial trials may not be ideal for functional food studies as they make use of both the intervention and placebo so there is a greater likelihood of confounding variables and "contamination" in results. This is a significant challenge in functional food studies as patients may inadvertently consume restricted foods containing the placebo during clinical trials. Therefore, randomized parallel-group trials and randomized cluster trials may be best for functional food studies as there is a reduced likelihood of the effects of one intervention being carried over to another intervention. Parallel-group

trials and cluster trials are based around similar concepts but differ in the number of people participating in the specific trial. Cluster trials may be particularly advantageous to functional food studies in that they provide the ability to study interventions that cannot be specified to individuals and reduce the chances of one individual's decisions affecting the rest of the study.

Overall, when planning clinical trials related to functional foods, researchers should consider alternative funding outlets, maintain close interactions with local industry partners, and use multiple biomarkers that may be unique to the specific functional food that is being evaluated. We conclude that randomized control trials, specifically randomized cluster trials and randomized parallel-group trials would be best for functional food trials because they provide information on the effects of a particular intervention and minimize the effects one intervention has on another intervention. By addressing challenges and overcoming them in functional food trials, researchers can better understand the role functional food has in prevalent chronic diseases and the definition of "functional food" may continue to evolve.

Abbreviations: CTA: Clinical Trial Applications; FOSHA: Food for Specified Health Uses; FDA: Food and Drug Administration

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