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Review Article

Common Study Designs of Nutrition Clinical Trials: Review of the Basic Elements and the Pros and Cons

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ABSTRACT

Introduction: Nutrition Clinical Trials (NCTs) are pivotal in establishing causal links between nutritional interventions and chronic diseases. This review comprehensively examines prevalent clinical trial designs, emphasizing their strengths and limitations. The goal is to provide insights into the selection and optimization of these designs for dietary intervention studies.
Methods: Various study designs in NCTs are explored, including quasi-experimental designs, double-blind randomized placebo-controlled trials for nutrient/functional foods supplementation, community-based lifestyle interventions, pragmatic nutrition interventions, and field trial projects. The characteristics, advantages, and challenges of each design are discussed. Real examples are presented to illustrate how these designs can be tailored and optimized for dietary intervention studies.
Results: Parallel randomized clinical trials are acknowledged as the gold standard, despite requiring substantial sample sizes and having inherent limitations. Cross-over NCTs emerge as valuable for assessing temporary treatment effects while mitigating potential confounders and interpatient variability. However, they may not be suitable for acute diseases and progressive disorders, and attrition rates can be higher. Multi-arm randomized designs offer increased study power with a lower sample size but necessitate more intricate design, analysis, and result reporting.
Conclusion: In conclusion, each study design in NCTs comes with its set of strengths and limitations. The selection of an appropriate design should consider determinants and common considerations to provide robust evidence for establishing cause-and-effect associations or assessing the safety and efficacy of food products in nutrition research. This comprehensive understanding aids researchers in making informed choices when planning and conducting nutrition clinical trials.

Introduction

As defined by the National Institute of Health (NIH), "clinical trial is defined as an experimental study, prospectively assigned human participants or groups of humans to

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one or more interventions, with or without concurrent comparison or control groups, to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes".[1] Nutrition clinical trials (NCTs) in which consumption of a nutrient, food, diet, or dietary behavior is altered in humans in a controlled way, and the effect on selected outcomes is measured, determine a cause-and-effect association, and provide a strong level of evidence.[2, 3] By conducting clinical trials, we can gather evidence to support or refute claims about the health benefits of certain nutrients or dietary patterns. Measurable patient-centered outcomes and appropriate study designs are needed. This evidence-based approach enables healthcare professionals and policymakers to make informed decisions regarding nutrition recommendations.[4-6]

NCTs are commonly used to provide strong experimental evidence to establish causal assosacion between diet and food components and health and disease,[2, 7] and help researchers and clinicians to determine how foods and diet can serve as effective tools for not only prevention but also management and treatment of diseases.[2] Historically, NCTs have been used for community-based interventions to solve public health problems;[2] the best examples are nutritional supports for protein-energy malnutrition,[8] iron supplementation or food-fortification for anemia, iodized-salt or seafood products for iodine deficiencies,[9] or vitamin A supplementation or food-fortification for xerophthalmia.[10] Health claims on food products, affirming causal association between foods and human health, also need to be confirmed by well-designed NCTs.[11] Furthermore, NCTs have broadly used either at the individual and community levels to change dietary behaviors to reduce the risk of chronic diseases; such well-known NCTs include the Bootheel Heart Health Project, the Minnesota Heart Health Program, and the North Karelia Project that primarily focused on cardiovascular risk reduction or The Women's Health Initiative (WHI) for prevention of breast and colorectal cancer.[12]

A wide range of NCTs is performed,[13] from a quasi-experimental study to a double-blind, randomized, placebo-controlled, nutrient/functional foods supplementation study,[11, 14, 15] a community-based lifestyle intervention,[8] nutrition education intervention,[16] or a population-based food fortification project.[17] NCTs are helpful in the development of personalized nutrition, addressing nutritional deficiencies and diseases, and evaluating safety concerns and adverse effects of a specific diet or supplements. They also provide a structured environment to assess the quality and standardization of nutritional products, ensuring that consumers receive safe and effective products with accurate nutritional content. In addition, NCTs have an essential role in forming nutritional guidelines.[18-20] Here we discuss how NCTs can be fitted to common clinical trial designs and how these designs can be optimized for dietary intervention studies to provide valid and reliable evidence, confirming the causal association, or safety and efficacy of food products.

Methods

In this review, we focus on the common clinical trial designs and their pros and cons and provide some real examples to discuss how these designs can be fitted and optimized for dietary intervention studies. Medline and

SCOPUS databases were searched until August 2023 without any time or language limitation. We used "clinical trial" OR "Clinical Trials as Topic" OR "Controlled Clinical Trial" OR "Clinical Study" OR "Research Design" OR "Pragmatic Clinical Trials as Topic" OR "Equivalence Trials as Topic" OR "Adaptive Clinical Trials as Topic" OR "Cross-Over Studies" OR "Multicenter Studies as Topic" OR "Randomized Controlled Trial"] OR "Non-Randomized Controlled Trials as Topic" OR "Single-Case Studies as Topic" OR "study design" OR "research methodology" as keywords for research design, and "nutrition" OR "nutrition trial" OR "nutrition intervention" OR "dietary intervention" OR "Nutritional Sciences" OR "Diet Therapy" OR "diet, food, and nutrition" as key words for nutrition science.

Results

NCTs must begin with a clear identification of the nutrition problem which needs to be addressed. A clear and explicitly specified study question or a well-defined hypothesis with the specific outcome(s), effectively points toward the best-fitted study design required for the development of the NCTs.[21, 22] The hypothesis should explicitly state how the food/ diet component would impact the primary outcome measures. Trying to answer several questions within one clinical trial is not recommended, however, If, the study follows secondary or tertiary objectives, the design and sampling methods need to be adopted to respond to additional study questions.

Depends on the study hypothesis/aim (i.e. assessing a cause-and-effect or safety and efficacy), the focus of interest (i.e. a particular nutrient, whole food, food group, whole diet, food supplement, change of behavior), the participant's characteristics and study setting (i.e. free-living healthy individuals vs. critically ill patients), the scale (individual vs. large community-based population) and the time required to observe the expected effects, different study designs may be used for NCTs.[3, 11, 13, 14, 23, 24] The stages of the translation research process (T1 to T4) also determine which design of NCTs needs to be considered. In T1 and T2 stages, researchers may focus on laboratory experiments and preclinical studies to identify promising nutritional interventions and gather preliminary evidence of their effectiveness and safety. In T3, researchers conduct clinical trials to assess the interventions' efficacy and safety in human populations. In T4, researchers evaluate the real-world impact of the interventions on a larger scale, looking at population-level health outcomes.[25] The most important point that needs to be considered is whether assessing the intervention in a highly-restricted setting (i.e. efficacy) or assessing it in a real-world setting (i.e. effectiveness) is the matter.[26]

As an experimental study, designs of NCTs may generally be classified as non-randomized clinical trials (Quasi-experimental studies) and randomized controlled trials (RCTs).[27] Table 1 summarized common study designs used in NCTs. Similar to RCTs,[28] parallel and crossover designs may be the two common designs for randomized nutrition trials. Less common study designs of NCTs are controlled feeding design, self-selected diet design, sequential design, and single subject or "N-of-1" trials[29] (used to evaluate the utility of personalized nutrition interventions).[30] It must be considered that all the design can used in adults and children based on ethical issues.

Non-randomized NCTs (Quasi-experimental studies)

Quasi-experimental studies are conducted to assess the cause-and-effect between an intervention and an outcome; they can be similar to randomized clinical trials in design, but lack one or more key features of a true experiment e.g. absence of random assignment to the intervention and control group, or lacking control group.[31] Shadish et al. discuss 17 possible designs for quasi-experimental studies, falling into 4 categories i.e. quasi-experimental designs without control groups (before-after design), quasi-experimental designs that use a control group but no pre-test, those that use control groups and pre-tests, and interrupted time-series design (with multiple before-after measurements).[32] These designs are appropriate in case of logistic problems (e.g. difficulty of randomizing, low sample size) or ethical issues in randomization.[31]

In the case of nutrition interventions, the most prevalent designs used are single-arm studies (before-after design) and non-equivalent groups design (i.e. intervention and control group not created through random assignment), which are more fitted on public health trials, e.g. community-based nutrition interventions.[13] Quasi-experimental designs are also appropriate for exploratory studies and the evaluation of new unestablished nutrition interventions.[33] Uncontrolled trials (single-arm or before-after studies) in NCTs have been preferred in situations where lack of intervention is an unethical practice, e.g. in malnourished or critically ill patients, pediatrics, or in diseases with rapid or fatal progression.[33]

The lack of randomization or control group is an important limitation of the quasi-experimental designs that threaten internal validity and establish the causality of the study.[32] Although quasi-experimental designs are less valued compared to randomized experiments in case of internal validity, they are acceptable for real-world practice and community-based research, where external validity is the matter.[21] Compared to a randomized trial, before-after interventions are suffering from the uncertainty of results, critically caused by lacking a control group to distinguish the actual effect of intervention from a natural trend of disease (for diseases have spontaneous improvement), potential selection bias of the participants, or placebo effects.[34] Regardless of these limitations, quasi-experimental designs can be used for low-prevalent cases, extremely small sample sizes, ethical concerns for random placebo assignment, or in the case of diseases with uncommon spontaneous improvement.[35]

Randomized NCTs

A randomized clinical trial (RCT) is an experiment conducted based on randomization, in which the experimental group receives an active intervention, and the control group receives an alternative treatment (e.g. placebo, standard treatment).[36] Randomization reduces the likelihood of bias, a systematic tendency of factors related to study design, conduct, analysis, and interpretation of findings.[37] Different types of randomization are defined i.e. simple randomization, block randomization, stratified randomization, and adaptive randomization, which can be generated using various statistical methods.[38]

During the last two decades, randomized NCTs have provided new insights for the use of clinical nutrition as supportive to other

treatments or as the primary intervention; compared to non-randomized interventions, randomized NCT designs are foundational to provide more reliable evidence for dietary guidance and public health strategies.[39]

The RCT design is usually recommended to be used as the gold standard for assessing the efficacy and safety of food-derived products, claiming specific health outcomes.[11, 40] Some discuss that RCTs however do not completely fit in but can be optimized for assessing the safety and efficacy of functional foods[7] and clinical studies of nutrient effects.[14] In contrast, some argue that RCT designs have fundamental limitations in nutrition research and often yield ambiguous results.[41] Although RCTs can be used for 'whole-diet' interventions (like those used by the large-scale trial e.g. Women's Health Initiative Dietary Modification and the PREDIMED trial), such designs are usually fit on a single food or a single nutrient or ingredient.[42]

Parallel versus cross-over design in NCTs

In a parallel design, participants receive only one of the nutrition interventions (e.g. vitamin E vs. placebo, or low-fiber diet vs. high-fiber diet) during the study period; comparisons between groups would be therefore on a between-participant basis.[13] In contrast, in a cross-over trial recruited participants to receive all interventions in a random order and all participants are considered as their controls;[43] the simplest model is the two-sequence cross-over trial (AB/BA study), where participants assigned to the AB study arm receive treatment A first, followed by treatment B, and vice versa in the BA arm.[43] The features of parallel and cross-over design are illustrated in Figure 1.

In a cross-over design, the potential effects of confounders and inter-individual variations are

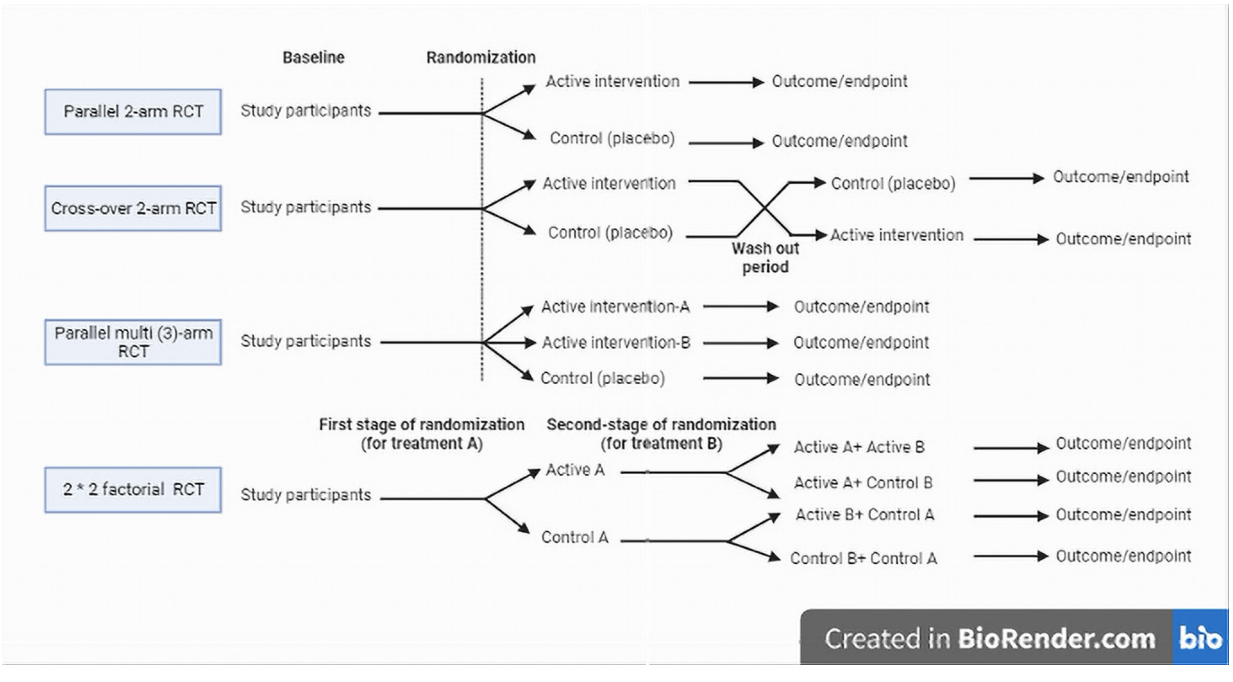

Figure 1. The features of parallel randomized clinical trial, cross-over randomized clinical trial, multi (3)-arm randomized clinical trial, and 2 × 2 factorial design randomized clinical trial.

effectively minimized.[35] Cross-over designs, however, are not appropriate for short-term outcomes in chronic diseases or diseases with unstable processes, since the disease or process needs to be persistent long enough, enabling researchers to assess the response of each participant to all experimental treatments.[43, 44] In a cross-over RCT, all participants have the opportunity to try all study interventions, and a potentially shorter recruitment period is needed for the study.[45] Such design provides the possibility of a within-participant basis for comparisons between interventions, improves the precision of comparisons, improved the study power, and decreases the required sample size.[13]

Compare to parallel trials, cross-over designs need longer duration and may not be fitted for incorporating multiple dosage arms, and may deal with a higher rate of drop-outs; there is also potential for un-blinding when the effects of the active intervention are more obvious to the participants than those of placebo.[37, 46] The main limitation of a cross-over design is the possibility of carry-over effects, defined as "the effect of the intervention from a previous time on the response to the following time".[35] Accordingly, one of the drawbacks of cross-over design is that an efficient washout period is needed between the study phases;[35] depending on the type of nutrition intervention and outcome measure, an optimized washout period needs to be defined to avoid contamination and minimize carry-over effects.[13] The 'potential order effects, where the order of interventions dependently manipulates the outcome or affects the participant's behavior, may also cause misinterpretation; both the 'practical effect' (i.e. a better performance in the second intervention because of the participant's knowledge) and fatigue effect (i.e. a worse performance in the second intervention due to participant's exhaustion) can occur in a cross-over experiment.[35] For more details on potential confounding variables in the cross-over design, the analysis and interpretation of cross-over data, sample size calculations, and application of cross-over designs in nutrition and dietetics, referring to Harris et al.[47] is highly recommended.

Multi-arm randomized NCTs

Besides convenient 2-arm RCTs (i.e. treatment arm and the control arm), multi-arm RCTs are relatively new designs that allow multiple interventions are simultaneously assessed against a single control arm.[48] The multi-arm RCTs outweigh two-arm designs because only a single control group (shared control) is needed for multiple interventions, and the total sample size is minimized.[49] A multi-arm trial compares multiple experimental treatments in a head-to-head manner within the same study;[49] in that case, concurrent assessment of a new intervention increases the chances of finding an effective intervention.[50] Using a multi-arm trial several hypotheses, including a comparison of multiple active interventions, assessing dose-dependent effects, assessing synergistic effects of interventions, simultaneous comparison of an intervention against a placebo, no active intervention, or standard treatment, can be tested.[51] The feature of a simple 3-arm clinical trial is illustrated in Figure 1.

The simple statistical approach in multi-arm settings is 2 or more specific pairwise comparisons of the treatments (comparing A vs. control, B vs. control, A vs. B, or in a 3-arm trial); more complex approaches can

be considered e.g. overall test of significance across comparison groups (comparing A vs. B vs. control in a 3-arm trial) which addresses variation in efficacy of several interventions or modeling a dose-response relationship.[51] Because multi-arm trials evaluate multiple hypotheses, statistical correction should be used to control the chance of type-1 error (false-positive).[52] There are some examples of muti-arm RCT in nutrition. In TAME trial, 225 children with SAM were divided into four intervention group; budeson ide, bovine colostrum, or N-acetyl glucosamine given orally or via nasogastric tube, or teduglutide given by subcutaneous injection and were compared by standard treatment.[90] In POUNDSLOST trial, 424 overweight adults were given four diets (I:20%fat-15%pro) (II:20% fat-25%pro) (III:40% fat-15% pro) (IV:40% fat-25% pro) to compare weight change among them.[91] These setting are helpful whenever we want to evaluate multiple nutrition treatments or intervention in a single disease setting, or having lower sample size.

Partially and fully randomized preference designs in NCTs

In contrast to standard randomized design, distributing characteristics of study participants equally without considering their preferences, some modifications have been made to incorporate the preference of the participant.[26] Due to the complexity of lifestyle interventions (e.g. diet interventions), alternative randomized study designs may be more practical.[26] Since such an approach influences the estimated effect sizes, which can be even larger than the direct effect of the intervention, preference randomized designs have been developed to effectively cover the problem.[53] Such designs are a combination of the best elements of RCTs, including random allocation of different treatments to willing patients, and feasibility studies, in which patients can opt for their preferred treatment.[53]

Partially randomized preference trial (PRPT) designs (categorized as Zelen design, Wennberg, Rucker, and Brewin designs[26]) have been provided as practical and useful alternatives of randomized study designs, where the intervention of interest may be affected by the subject's presences.[53] A PRPT design provides recruited participants the option to choose their desired treatment (e.g. preferred diet), and if the patients have no interest in a specific treatment, they would be randomly assigned to one or another treatment.[53] An alternative approach is a fully randomized preference design, in which after participants have given consent in the usual way and before randomization, patients' preferences are recorded; this design then takes into account preferences in the analysis of the trial.[54, 55]

The impact of patient preferences on dropout rate and the outcome is not fully addressed, however, the Preference Collaborative Review Group determined the issue using a meta-analysis of clinical trials and reported that patients who were randomized to desired treatment had an increased treatment effect compared with those who had no chance to opt their treatment assignment.[55] An important disadvantage of the PRPT design is that the comparability of the non-randomized and non-randomized groups is debatable.[55, 56] It should be noted that all participants recruited into the preference randomization, should be asked to provide clear, accurate, and detailed reasons about their treatment preferences.[53] In the

field of nutrition, PRPT design maybe useful in diet therapy; adherence of patients might be increased if their preferences considered. In PREFER trial, 182 overweight adults were divided into two groups based on participants' preference; calorie- and fat-restricted diets [standard behavior treatment (SBT) and lacto-ovo-vegetarian ([SBT+LOV)]. Finally, they compared based on anthropometric parameters and behavior weight management.

Factorial design in randomized NCTs

Factorial experiments assess the effect of more than one treatment (factor) using a design enabling assessment of interactions between the treatments; such designs are highly valuable because of providing an opportunity to evaluate multiple intervention components with good statistical power and detect potential interactions of the interventions.[57, 58] A full factorial design with k factors (k is the number of treatments), each comprising two levels, contains 2k combinations of factor levels;[58] each of the 2k cells in the design corresponds to a group of participants assigned to a specific combined treatment.[59] Common designs of RCT are single-factor experiments with two levels including 'an active treatment' and a 'control condition'.[58] The feature of a 2 × 2 factorial design is illustrated in Figure 1.

To apply factorial design some important questions need to be addressed by the researchers, which include "how many and which type of factors would be considered", "how the compatibility of the different factors would be addressed", "whether and how confounds between the type and number of interventions would be avoided, and how the interactions would be interpreted".[58] It also should be noted that factorial designs cannot be optimally fitted where there are weak main effects for the factors, but relatively strong interaction effects;[59] other common concerns about factorial design are cost, feasibility, ethics, possible toxicity of combined treatments, interpretation of main effects in presence of active interactions, and concern about power for detecting interactions.[59] This type of study is more applicable in the reality that two or more unrelated interventions are considered. For example, in CENEX trial, 2800 elderly were divided into 4 group to compare different effects of nutrition and exercise intervention. Group I was nutrition intervention alone (a cereal-legume and vegetable powdered food and a milk-based powdered drink), group II was exercise alone (2 sessions per week), group III was nutrition + exercise, and, group IV was control. Pneumonia incidence and walking capacity were assessed in this trial.[94] In WACS study, 8171 females with a history of CVD or 3 or more CVD risk factors were included into 2*2*2 factor trial (vitamin C, vitamin E, β-carotene). Myocardial infarction, stroke, coronary revascularization, or CVD death in 10-year were assessed.[95]

Cluster-randomized mixed NCTs

Cluster randomized trials (CRTs) include groups (clusters) randomization of individuals to control or intervention of interest; the such design is commonly used to evaluate non-drug interventions, such as policy and service delivery interventions.[60, 61] The unit of randomization in this design is not the individual but a cluster of individuals defined, e.g. family, school, or primary care group.[13] The advantages and disadvantages of cluster design was summarized

in Table 1. In this design larger numbers of individual participants are needed to obtain the same statistical power. Also, the hierarchical nature of cluster randomized trials can lead to a duplication of upstream preparation and sensitization efforts. There are some examples in nutrition studies; Nutrition, health, hygiene Bangladesh study was an example of NCTs.[96] In this study, 48 clusters in 2 rural regions, in Bangladesh were included in a factorial design and were given water-based hand sanitizer+ micronutrient power to decrease stunting in low-birth-weight infants. In MAHAY trial, 1250 children 0-6 months old, and 6-18 months in 5 regions in Madagascar were taking a multi-arm intervention.[60] Interventions include monthly growth monitoring and nutritional/ hygiene education, home visits for intensive nutrition counseling within a behavior change framework, and lipid-based supplementation for children. Growth (length/height-for-age z-scores) and child development (mental, motor, and social development) were compared.

Pair-matched randomized NCTs

Pair-matching is a strategy used in randomized trials to improve their validity and study power; such designs keep the balance of treatment groups concerning important determinants of the outcome at baseline.[62] The participants in the study groups are matched in pairs on a person-to-person basis for variables e.g. age and sex, and then are randomized to active treatment and control. Pair-matched design is usually used for cluster randomization, within which clusters (communities) were put into pairs and one cluster of each pair was randomly allocated into the treatment group.[63] There are some examples in this regard. In ACTIVITAL trial, 10 pair school (1430 adolescents) were included in diet intervention+ physical activity to control abdominal obesity.[97] In WASH Benefits study, pregnant women in a rural region had educational classes for improvements in water quality, sanitation, handwashing, and child nutrition.[98] Child length-for-age Z-scores and caregiver-reported diarrhea in Kenya were compared to find the intervention effects.

Pragmatic randomized NCTs

Pragmatic randomized clinical trials (PrCTs) is a combined design of a real-world setting and randomization, which is used to evaluate treatment effectiveness and healthcare decisions; such design can help to answer the important question of 'how a treatment works in a real-world scenario',[64, 65] and thereby maximizes the external validity of research findings.[21] The main features of pragmatic trials are using alternative interventions compared to standard treatment, including diverse populations, selecting study participants from heterogeneous settings, and considering different health outcomes.[21] The use of pragmatic clinical trial design can facilitate translational research findings and accelerate integration into practice and policy.[66]

To fit the trial as "explanatory RCT" or "pragmatic RCT", a nine-domain tool (PRECIS-2), has been developed to score the degree of pragmatism of the RCT, which ranges from very explanatory to very pragmatic.[67] Some practical guides, which researchers need to take into careful consideration to minimize major potential bias and optimize the design of pragmatic clinical trials, are provided by Caro et al.[68]

Pragmatic design is mostly used to investigate

Table 1. The pros and cons of using common designs of clinical trials for nutrition interventions

Study design	Definition	Examples	Strengths	Limitations
Non-randomized design (Quasi-experimental design)	Similar to randomized clinical trials in design, but lack one or more key features of a true experiment	GReat-Child Trial [82, 83] TP: Children aged 9 to 11 years in two primary schools (without randomization) IG: Whole grain & education lessons CG: Health recommendations PO: Manage childhood obesity (BMI/age) Back 2 Balance [84, 85] TP: Low-income multi-problem households IG: Enhance healthy nutrition, physical activity, and social network CG: Usual services (without randomization) PO: Self-perceived health	• Appropriate for exploratory studies, evaluation of novel, and untested dietary interventions • Appropriate when not providing an intervention is unethical (e.g. in high-risk patients) • Valuable for real-world practice and community-based nutrition intervention	• Lack of random assignment (or control group) • Has low internal validity and low power to establish causality • Results may be limited by low signal and high noise • Difficult interpretation due to several potential confounding effects
Parallel randomized design	Participants received intervention or control. Both groups run simultaneously.	PREVENTOMICS [86] TP: 82 overweight/obese adults IG: Personalized diet CG: Control diet based on American guidelines PO: Weight change NuEva study [87] TP: 110 healthy adults IG: A plant-based diet CG: Traditional Western diet PO: LDL & HDL cholesterol	• Gold standard for assessing efficacy and safety of food-derived products claims • Straightforward • Has clear temporal sequence, internally valid comparison	• Needs a large sample size compared to a cross-over design • Has fundamental limitations in nutrition research (e.g. for whole diet intervention, change of dietary behavior) i.e. impossible blinding, use of placebo • Its external validity and generalizability are limited
Cross-over randomized design	Participants received both control and intervention treatment	DELTA [88] TP: 85 overweight adults IG: MUFA diet/ CHO diet CG: average American diet PO: weight changes OmniHeart trial [89] TP: 164 adults with prehypertension IG: CHO diet/ PRO diet CG: USF diet PO: SBP & LDL cholesterol	• Useful when treatment effects are temporary and baseline levels are achievable when the dietary manipulation is removed • Reduces influence of potential confounders and interpatient variability	• Not useful for acute diseases and progressive disorders • Has a higher attrition rate • Needs longer duration and may not be fitted for incorporating multiple dosage arms • Needs appropriate washout period between study phases • May be affected by carry-over effects or potential order effects of the interventions

Table 1. (continued)

Study design	Definition	Examples	Strengths	Limitations
Multi-arm randomized design	Multiple interventions are simultaneously assessed against a single control arm	TAME trial [90] TP: 225 children with SAM IG: Four novel interventions (budesonide, bovine colostrum, or N-acetyl glucosamine given orally or via nasogastric tube, or teduglutide given by subcutaneous injection) CG: Standard treatment PO: Malnutrition POUNDSLOST [91] TP: 424 overweight adults IG: Four diets (I:20%fat-15%pro) (II: 20% fat-25%pro) (III:40% fat-15% pro) (IV:40% fat-25% pro) PO: Weight changes	• Evaluate multiple treatments in a single disease setting • Lower sample size required • Increased study power	• Can be more complex in their design, data analysis, and result reporting than two-arm trials • May increase type 1 error
Randomized preference designs	Randomization is based on participants' preferences	PREFER trial [92, 93] TP: 182 overweight adults IG: Calorie- and fat-restricted diets [standard behavior treatment (SBT) and lacto-ovo-vegetarian ([SBT+LOV)] based on participants' preference PO: Behavioral Weight Management	• Provides an efficient way for randomized study designs, where the intervention of interest is affected by the subject's preferences • May increase adherence rate and treatment effect	• The outcome may be affected by uncontrolled confounders in the non-randomized groups
Factorial design	Assess the effect of more than one treatment (factor) using a design enabling assessment of interactions between the treatments	CENEX trial [94] TP: 2800 elderly IG: 2*2: I: Nutrition intervention alone (a cereal-legume and vegetable powdered food and a milk-based powdered drink), II: Exercise alone (2 sessions per week), III Nutrition + exercise, and, IV: Control. PO: Pneumonia incidence and walking capacity WACS study [95] TP: 8171 females with a history of CVD or 3 or more CVD risk factors IG:2*2*2 (vitamin C, vitamin E, β-carotene) PO: Myocardial infarction, stroke, coronary revascularization, or CVD death in 10-year	• Enables efficient evaluation of multiple treatments and their potential interaction	• Difficult interpretation of main treatment effects when interaction exists

Table 1. (continued)

Study design	Definition	Examples	Strengths	Limitations
Cluster design	Include groups (clusters) randomization of individuals to control or intervention of interest	MAHAY trial [60] TP: 5 regions in Madagascar (1250 children 0-6 months old, and 6-18 months) IG: Multi-arm intervention (monthly growth monitoring and nutritional/hygiene education, home visits for intensive nutrition counseling within a behavior change framework, lipid-based supplementation for children) PO: Growth (length/height-for-age z-scores) and child development (mental, motor, and social development) Nutrition, health, hygiene Bangladesh study [96] TP: 48 clusters in 2 rural regions, in Bangladesh IG: 2*2: Water-based hand sanitizer+ micronutrient power PO: Decrease stunting in low-birth-weight infants	• Intervention conducted at group level • Policy or service delivery interventions. • Evaluate study interventions that cannot be directed toward selected individuals. • Sometimes is easier than individual interventions.	• Greater complexity of their design • Need to include larger numbers of individual participants to obtain the same statistical power • The hierarchical nature of cluster randomized trials can lead to a duplication of upstream preparation and sensitization efforts
Pair-matched design	Participants are matched in pairs on a person-to-person basis for variables e.g. age and sex, and then are randomized to active treatment and control	ACTIVITAL trial [97] TP: 10 pair school (1430 adolescents) IG: Diet intervention+ physical activity PO: Abdominal obesity WASH Benefits study [98] TP: Pregnant women in a rural region IG: Improvements in water quality, sanitation, handwashing, and child nutrition PO: Child length-for-age Z-scores and caregiver-reported diarrhea in Kenya	• Improve validity and study power. • Keep the balance of treatment groups concerning important determinants of the outcome at baseline • There is less variability found in results, and it can be applied to most diseases. • Usually used in a cluster design	• Based on similarity within the selected groups, the researcher needs awareness of factors that could influence results (confounding variables).

Table 1. (continued)

Study design	Definition	Examples	Strengths	Limitations
Pragmatic randomized design	A combined design of a real-world setting and randomization, which is used to evaluate treatment effectiveness and healthcare decisions	NOW trial [99] TP: 140 obesity clinics IG: Individuals- based intervention CG: A population-based intervention PO: Dietary intake and weight changes HEPAPP trial [100] TP: 131 childcare services IG: Increase healthy eating and physical activity-promoting policies PO: Adherence to healthy activity	• Indicates how a treatment works in a real-world setting • Facilitate translational research findings into practice and policy • High external validity • Usually, alternative interventions compared to standard treatment	• Low internal validity • Needs large sample size, human and construction support • Expensive
Adaptive designs	A study with the prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data)	PREDIMED-Plus [101] TP: 6874 men and women aged 55 to 75 years with metabolic syndrome and no cardiovascular disease IG: Energy-reduced Mediterranean diet, promoted physical activity, and provided behavioral support CG: Energy-unrestricted Mediterranean diet PO: 12-month change in adherence based on the energy-reduced Mediterranean diet (er-MedDiet) score Healthy Mom Zone trial [102] TP: Overweight and obese pregnant women IG: Education (i.e. dietary and physical activity), goal-setting, self-monitoring, and active learning CG: Standard of care PO: Manage gestational weight gain and fetal growth	• Allow continual modifications to key components of trial design e.g. allocation ratio, total sample size, eligibility criteria, an extension of trial phases, change of treatment arms, dose and intervention tensity, and study duration • Increases the efficiency of conventional designs • Helps researchers with a more flexible and faster clinical development process	• Complex designs, complex analysis, and operational challenges • Additional cost and resources to build adequate infrastructure • Potential missing important secondary information

Table 1. (continued)

Controlled feeding design	All foods and fluids are provided to participants	The DASH diet [103] TP: 459 healthy adults IG: Vegetable & fruit diet/ ideal diet (low-fat dairy products, fish, chicken, and lean meats to decrease saturated fat and increase protein and calcium) CG: American diet PO: Systolic and diastolic blood pressure Delta Study [104] TP: 103 healthy men and women IG: Three diet plans with different macronutrient percentages (26%, 30% & 37% fat) PO: Plasma Lipids and Lipoproteins	• Determine cause-and-effect associations between dietary intake and physiological or health outcomes • The ability to perform deep phenotyping	• Time- and resource-intensive design • Need human and technical support • Expensive
Self-selected diet design	Participants choose which group to take part	Diet CVD trial [105] TP: 560 healthy adults IG: A self-selected mixed-food plan and a nutrient-fortified prepared meal plan PO: Dietary compliance and cardiovascular outcomes	• Supported individual's autonomy and increased perception of control over behavior • Resulting in positive adherence, competence, and self-efficacy, essential attributes for a long-term successful lifestyle change • Translating findings to the community might be easier.	• Selection bias might affect the results • Confounders effects might change findings
Sequential design	The sample size of the trial is not fixed in advance, and data is sequentially evaluated as it is collected	DASH series [78] DASH dietary pattern, sodium trial, PREMIER trial, OPOD trial [106] TP: Obese candidate surgery IG: Obese preoperative diet PO: Nutrition intervention after laparoscopic bariatric surgery	• Allow early termination of the trial for evidence of benefit, harm, or equivalence • Evaluate responses to a nutritional intervention within different degrees of experimental control • Explanatory • Improve efficiency and cost-benefit of RCTs and increase the chance of finding a true treatment effect	• Expensive • Needs technical and construction support • Long term

Table 1. (continued)

Study design	Definition	Examples	Strengths	Limitations
N-of-1 trial	A patient receives intervention and control treatments	WE-MACNUTR trial [107] TP: 1 person IG: A 6-day high-fat, low-carbohydrate (HF-LC) diet and a 6-day low-fat, high-carbohydrate (LF-HC) diet PO: Provide personalized dietary recommendations on macronutrients in terms of post-prandial blood glucose response	• Use in an uncertain situation • Use in chronic, stable, or slowly progressive conditions that are either symptomatic or for which a valid biomarker has been identified • Treatments to be assessed in n-of-1 trials should have a relatively rapid onset and washout	• Rapidly progressive conditions (or those prone to sudden, catastrophic outcomes such as stroke or death) are not amenable to the deliberate experimentation of n-of-1 trials

TP, Target population; IG, Intervention group; CG, Control group; PO, Primary outcome

changes in the health system and health policy in nutrition. In NOW trial, 140 obesity clinics were compared how individuals- based intervention worked instead of a population-based intervention to change dietary intake and weight.[99]

In HEPAPP trial, 131 childcare services were compared by increaseing healthy eating and physical activity-promoting policies.[100]

Adaptive designs in randomized NCTs

The US Food and Drug Administration (FDA) defines an adaptive clinical trial as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study".[69] Adaptive designs improve the efficiency and cost-benefit of RCTs and increase the chance of finding a true treatment effect.[70]

Both exploratory and confirmatory RCTs can be fitted into adaptive designs; for exploratory RCTs, adaptive designs deal with the safety and efficacy of doses or dose-response modeling.[71]

Adaptive designs are categorized as:

1) adaptive randomization design,
2) group sequential design,
3) sample size re-estimation design,
4) drop-the-losers design,
5) adaptive dose-finding design,
6) biomarker-adaptive design,
7) adaptive treatment-switching design,
8) hypothesis-adaptive design,
9) adaptive seamless trial design, and
10) multiple adaptive design.[71, 72] Details of the rationale and designs of adaptive clinical trials have been discussed elsewhere.[71, 73]

Some adaptive clinical trial designs are recently considered to develop nutrition intervention studies;[42, 72] these designs differ from conventional clinical trials and allow continual modifications to key components of trial design (e.g. allocation ratio, total sample size, eligibility criteria, an extension of trial phases, change of treatment arms).[73] The use of adaptive designs helps researchers with a more flexible and faster clinical development process.[74]

Specific complex designs in NCTs

All specific complex designs in NCTs are presented in Table 1. These designs are less common in NCTs and have less real exmples.

Controlled-feeding design

The 'controlled-feeding design' is a specific design for controlled NCTs, in which "all foods and fluids are provided to participants and the placebo group receives a diet to be 'inert' in nature, and nutritionally matched to the intervention diet in all aspects except for the active component being investigated".[33, 75] Since controlled feeding is a time- and resource-intensive design, available resources including human and technical support to design controlled diets, food supplies, food preparation, and storage equipment, should be considered.[75] More details regarding the design, conduct, and pros and cons of controlled feeding have been extensively discussed by Davy et al .[75] In the DASH diet trial, 459 healthy adults were consumed vegetable & fruit diet or ideal diet (low-fat dairy products, fish, chicken, and lean meats to decrease saturated fat and increase protein and calcium) or American diet to find effects of diets on systolic and diastolic blood pressure.[103] In Delta Study, 103 healthy men and women were consumed three diet plans with different macronutrient percentages (26%, 30% & 37% fat) to clear effects of dietary fat on plasma lipids and lipoproteins.[104]

Self-selected diet study design

Free-living self-selected diet study design, which is commonly used for weight loss trials among free-living participants, may be considered a well-known PRPT design in NCTs; free-living, self-selected NCTs are usually more successful with close participants monitoring and findings of these studies are closer to real-world settings.[76] In a Diet CVD trial, 560 healthy adults were given a self-selected mixed-food plan and a nutrient-fortified prepared meal plan to assessed dietary compliance and cardiovascular outcomes.[105]

Sequential designs in NCTs

Sequential study designs allow early termination of the trial for evidence of benefit, harm, or equivalence; these designs include fully sequential designs, group sequential designs, and flexible sequential designs.[77] The flexible sequential design may be a more suitable compromise for most trials and is being widely used.[77] The NCTs may usually perform sequential designs, in which a series of related studies are conducted that evaluate responses to a nutritional intervention within different degrees of experimental control.[78]

In sequential intervention series, initial experiments frame the questions for subsequent studies and may be considered an explanatory trial. Such designs are used to initially determine the efficacy (i.e. the maximum effect of the interventions in a controlled feeding setting) of the first intervention, and then determine the effectiveness (i.e. the magnitude of intervention effects attainable in the free-living environment) of the last intervention.[78] DASH dietary pattern series is an example of sequential trials.[78] In these trials effects of sodium and dietary pattern for decreasing blood sodium levels and hypertension were assessed.

OPOD trial is another example for sequential design.[106] In these trials the best nutrition and diet intervention after laparoscopic bariatric surgery were assessed.

Single subject or "N-of-1" trial in NCTs

An N of 1 trial is a clinical trial in which a single patient is an entire trial. In an N-of-1 trial, a patient receives treatments in pairs (one period of the experimental therapy and one period of either an alternative treatment or placebo, in random order), both patient and clinician are kept blind to allocation, and treatment targets are monitored.[79] This type of RCT is useful in chronic, stable conditions in which the proposed treatment has a short half-life. Treatment targets usually include quantitative measurement of symptoms tracked through patient diaries.[80] Pairs of treatment periods are continued until effectiveness is proven or refuted. The N of 1 RCT is the potential of great use in psychopharmacology and drug development.[80, 81] In a N of 1 trial WE-MACNUTR trial, effect of a 6-day high-fat, low-carbohydrate (HF-LC) diet and a 6-day low-fat, high-carbohydrate (LF-HC) diet on postprandial blood glucose response were assessed for providing personalized dietary recommendations.[107]

Conclusion

During the last two decades, NCTs have provided invaluable and reliable evidence for clinical practices indicating the importance of diet in prevention of chronic diseases and modulation of potential risk factors. NCTs have yielded strong evidence for a cause-and-effect association between diet and diseases and led to evidence-based guidelines for dietary patterns and nutrient intakes. This impressive progress in the field of nutrition has resulted from both common study designs of clinical trials and the use of more complex and specific study designs of nutrition interventions. Well-designed NCTs need to be developed by interactive communications between public health scientists and policymakers to ensure they would be practical in real-world settings and they are cost effectiveness. As the manuscript is a narrative review, there are some limitations that must be considered. Narrative reviews may be subject to bias in the selection of studies to include. In this review, the authors rely on the published studies. Unlike systematic reviews, narrative reviews may not follow a rigorous and transparent search and inclusion process. This could result in overlooking relevant studies or excluding some that could provide valuable insights. They often cover a broad range of topics but may lack the in-depth analysis provided by systematic reviews. As a result, some aspects of nutrition clinical trial designs may not receive sufficient attention or exploration. To sum up, the development of more complex research designs and performing optimized conventional RCT designs are critical to advance the field of clinical nutrition.
Determinants and common considerations need to be considered to adopt an appropriate design for NCTs, providing robust evidence in case of a cause-and-effect association or assessing the safety and efficacy of food products.

List of abbreviations

NCTs, Nutrition clinical trials;

RCTs, Randomized controlled trials;
CER, comparative effectiveness research;
PRPT, Partially randomized preference trial;
ATBC, Alpha-Tocopherol Beta-Carotene Cancer;
CRTs, Cluster randomized trials;
MNP, Mineral- and vitamin-enhanced micronutrient powder;
PrCTs: Pragmatic randomized clinical trials;
FDA, Food and Drug Administration;
DGA, Dietary Guidelines for Americans;
TAD, Typical American diet;
ADA, American Diabetic Association;
NCEP/AHA, National Cholesterol Education Program and American Heart Association;
OPOD, Obese preoperative diet;
ADMF, Alternate day modified fasting;
NIHR, National Institute for Health Research https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5894808/?report=classic - bibr14-1740774517752113;
MM, Michigan Model;
SHINE, Hygiene Infant Nutrition Efficacy;
MRC, Medical Research Council;
ICH, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

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Z.B., H.M, and P.M. developed the concept, critically reviewed the literature, and wrote the manuscript.

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