Optimizing clinical nutrition research: the role of adaptive and pragmatic trials

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Abstract

Evidence-based nutritional recommendations address the health impact of suboptimal nutritional status. Efficacy randomized controlled trials (RCTs) have traditionally been the preferred method for determining the effects of nutritional interventions on health outcomes. Nevertheless, obtaining a holistic understanding of intervention efficacy and effectiveness in real-world settings is stymied by inherent constraints of efficacy RCTs. These limitations are further compounded by the complexity of nutritional interventions and the intricacies of the clinical context. Herein, we explore the advantages and limitations of alternative study designs (e.g., adaptive and pragmatic trials), which can be incorporated into RCTs to optimize the efficacy or effectiveness of interventions in clinical nutrition research.

Efficacy RCTs often lack external validity due to their fixed design and restrictive eligibility criteria, leading to efficacy-effectiveness and evidence-practice gaps. Adaptive trials improve the evaluation of nutritional intervention efficacy through planned study modifications, such as recalculating sample sizes or discontinuing a study arm. Pragmatic trials are embedded within clinical practice or conducted in settings that resemble standard of care, enabling a more comprehensive assessment of intervention effectiveness. Pragmatic trials often rely on patient-oriented primary outcomes, acquire outcome data from electronic health records, and employ broader eligibility criteria. Consequently, adaptive and pragmatic trials facilitate the prompt implementation of evidence-based nutritional recommendations into clinical practice.
Recognizing the limitations of efficacy RCTs and the potential advantages of alternative trial designs is essential for bridging efficacy-effectiveness and evidence-practice gaps. Ultimately, this awareness will lead to a greater number of patients benefiting from evidence-based nutritional recommendations.

Introduction

Suboptimal nutritional status contributes to the development and progression of chronic diseases and predicts mortality[1–3]. Inadequate energy and nutrient intakes are hallmarks of suboptimal nutritional status and are associated with low muscle mass and malnutrition, which are prevalent among older adults and patients with acute or chronic diseases[4–6]. Although the pathophysiology of these conditions is multifactorial, adequate energy and nutrient intakes are essential for optimizing health outcomes. As such, alterations in dietary patterns, food and/or supplement intake have been explored to improve nutritional status and minimize the impact of related conditions[7,8].

Historically, nutritional recommendations addressing the health consequences of suboptimal nutrition have been derived from evidence collected using various sequenced research designs (**Figure 1**)[9]. Prior to incorporating nutritional interventions in clinical practice, randomized controlled trials (RCTs) are carried out to assess intervention efficacy and effectiveness, which exists along a continuum[10–12].

Efficacy RCTs, also known as exploratory trials, are common in nutrition research, as they are designed to evaluate the causal effects of nutritional intervention on health outcomes, while controlling for confounding variables, under ideal circumstances[13–15] (**Table 1**). However, clinical conditions and nutritional interventions are complex and may interfere with the ability of efficacy RCTs to negate confounding effects, introducing challenges for data analysis and interpretation[13,16,17]. Efficacy RCTs also have inherent limitations, namely trial features cannot be changed after study initiation and implementation requires costly and complex infrastructures[13]. These drawbacks became more evident during COVID-19, as researchers had to modify ongoing trials to comply with evolving public health and safety measures.

The rigorous eligibility requirements and methodological diversity in efficacy RCTs pose additional challenges to nutrition research, including low recruitment rates and limited generalizability[14,16]. Convenience sampling is often used to enhance recruitment and can be a substitute for attracting the intended demographic. This use of a readily accessible population creates selection bias and may not accurately represent the target population[18]. Trial patients are often those who are most likely to respond positively to nutritional therapy; they are typically younger, with fewer comorbidities, and have superior nutritional status than those referred for nutritional care[16]. Nutritional interventions, outcomes assessments, and condition definitions lack uniformity, further complicating efficacy RCTs[7,19,20]. This can reduce the external validity of efficacy RCTs, further complicating the transformation of evidence into clinical practice, a phenomenon referred to as the evidence-practice gap[21,22].

Effectiveness RCTs, also known as pragmatic trials, assess the real-world relevance of findings derived from efficacy RCTs by employing an alternative design[11,12]. Such trials are conducted on larger, more diverse populations in less controlled environments to simulate real-world settings[23] and provide crucial information for clinical application. Nevertheless, a disparity in treatment effects between efficacy and effectiveness RCTs is often observed and known as the efficacy-effectiveness gap[23]. Although nutrition guidelines are typically established using evidence from systematic reviews and meta-analyses of RCTs, inconclusive findings are common due to stringent eligibility criteria, high methodological heterogeneity, inconsistent results, few trials with low risk of bias, and/or insufficient statistical power[7,19,20]. Hence, clinical nutrition guidelines often include expert consensus or observational study data, which are more prone to bias than RCTs[24–27].

More flexible and alternative methodologies, such as adaptive and pragmatic trials, provide a valuable avenue to address limitations of efficacy RCTs, bridge research gaps, and benefit patients and healthcare systems through the provision of evidence-based nutritional care (**Table 1**)[13]. Adaptive designs can be incorporated into RCTs to enhance intervention efficacy as they allow preplanned trial modifications to an ongoing study based on interim analysis (i.e., analysis of accrued data prior to trial completion)[28]. Hiremath et al.[29] employ an adaptive design to determine the most effective approach for increasing potassium intake in patients with hypertension. Patients first receive individualized nutritional counseling in line with current guidelines; non-responders receive potassium supplementation if interim analysis at week four reveals unmet intake goals, while responders continue with nutritional counseling alone for one year[29]. Modifications to an ongoing trial can enhance recruitment, dose-response assessment, precision of treatment effect estimates, and implementation[30]. As mentioned, pragmatic trials adopt a patient-oriented, real-world approach to assess intervention effectiveness within the routine patient care context[12]. Schuetz et al.[31] used a pragmatic design to evaluate a protocol-guided individualized nutritional support for patients at nutritional risk. This pragmatic design encompassed a larger, more diverse patient group; healthcare professionals delivered interventions tailored to patients' needs; comparisons were made with best available treatment modalities; study visits were integrated into routine clinical follow-ups; and patient-oriented outcomes were measured[12,31]. Pragmatic trials are designed to inform practitioners and policy/decision-makers of intervention advantages and limitations in a pragmatic setting, thus enabling swift integration of innovative nutritional therapies into standard clinical practice[32].

Adaptive and pragmatic trials are rigorous and provide high-quality data to establish and inform evidence for preventing and managing complex nutrition-related health conditions[12,28,33].

In this narrative review, we explore the potential for adaptive and pragmatic trials to advance the field of clinical nutrition research. We discuss common pitfalls of nutrition-focused efficacy RCTs and the impact of COVID-19 on clinical nutrition research. Key aspects of incorporating alternative designs into nutrition trials are examined, along with specific examples. We also propose the use of alternative designs in oncology nutrition research. Articles discussed here were identified in Medline, PubMed, or Google Scholar using keywords related to the following topics up to February 2023: strengths and weakness of efficacy RCTs; COVID-19 impact on research processes; study designs in clinical nutrition research; adaptive and pragmatic trials; and nutrition trials in oncology.

The Shortcomings of Efficacy RCTs in Nutrition Research

Efficacy RCTs are conducted in highly controlled settings using rigorous strategies from study development to data analysis[13–15]. These trials are preferred over observational studies in free-living conditions because, when properly used, they minimize bias from confounding factors and begin to establish a cause-and-effect relationship between an intervention and health outcome[13,34]. Reporting bias can be mitigated through intention-to-treat analysis, which assesses the efficacy of the assigned intervention irrespective of uptake[35]. Although intention-to-treat analysis is regarded as the standard for efficacy RCTs, these studies often include a per protocol analysis evaluating the effects of intervention adherence[10]. Randomization is another key feature of RCTs that minimizes bias by comparing baseline characteristics of groups and inferring treatment effect[13]. Among randomization approaches, stratifying patients based on similar prognostic factors—such as age, sex, and disease stage—results in more balanced groups but requires larger samples to maintain statistical power, especially with multiple strata[36]. Additional randomization-related issues are observed in nutrition trials, including failure to conceal allocation and/or to maintain allocation ratio, which can modify the cause-and-effect relationship[37].

Controlling for dietary intake is another challenge of efficacy RCTs[14,16]. Patients in these trials often receive nutritional interventions in designated clinical research units or are provided prepared meals for the entire, or partial, study duration. A controlled-feeding trial provides all meals for on-site or off-site consumption and allows for precise quantification of food composition while minimizing the confounding effects of usual diet[14,38]. Nevertheless, controlled-feeding trials rarely use appropriate nutrient analytics to assess dietary composition. Seasonality, soil, and stage of ripeness can influence phytochemical and nutrient composition of diets, affecting predicted effect or reproducibility of study results[39,40]. Controlled-feeding trials can be costly, burdensome to patients, and limited in their real-world applicability[14,38].

Blinding is common in efficacy RCTs but is not possible or practical in many nutritional interventions, particularly those that require patients to alter dietary intake, resulting in study arm contamination[14]. Nutritional supplement trials often use a double-blind design where both patients and outcome assessors are unaware of trial arm allocation[14]. Control arm patients receive a placebo supplement of similar taste, color, and consistency to the trial intervention, an approach viewed as more robust[41]. While dietary confounders can be managed by collecting usual dietary intake data and using nutritional biomarkers for adherence, these approaches can be costly and imprecise[42].

Efficacy RCTs have restrictive eligibility criteria aimed at excluding other known confounders such as comorbidities, medication use, habitual dietary patterns (including the use of supplements, botanicals, and herbals), exercise patterns, malabsorption disorders, and food allergies/intolerances that may modify outcome(s)[14,16]. However, these restrictive criteria can challenge recruitment goals and limit generalizability of findings to a more diverse population. For instance, RCTs examining the effects of nutritional supplements on outcomes of patients with cancer excluded those with a substantial weight loss history, and/or those with low performance status and comorbidities[43–45]. Although these trials provide evidence of the supplementation effects, their generalizability is unclear given the restrictive eligibility criteria.

Efficacy RCTs use precise and valid techniques to minimize measurement errors when assessing outcomes. Although these techniques are increasingly available, they are not universally used in clinical settings and are often reserved for research purposes. Efficacy RCTs can accurately quantify muscle mass and/or related compartments using body composition techniques, including dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and computed tomography; however, not all clinical settings have the capacity to employ them. Dietary exposure biomarkers, such as plasma carotenoids, urine polyphenols, fecal microbiome, and hair cortisol, are frequently used in research but are impractical in clinical settings due to high costs and complex laboratory analysis[42]. These techniques are gaining ground in clinical practice and aiding in closing this gap, though they may be restricted to specific settings. The absence of precise and valid techniques makes monitoring and evaluating of nutritional interventions difficult in clinical settings, with results potentially differing between techniques used in efficacy RCTs versus real-world clinical settings[46].

Efficacy RCTs are robust yet lack flexibility and are burdensome for patients[14]. These shortcomings are particularly relevant when trial protocol adjustments are warranted to mitigate extenuating circumstances, such as during COVID-19, strikes or regulatory changes[47]. Unplanned trial modifications can introduce bias that alters cause-and-effect relationships. The

CONSERVE 2021 (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances) statement was released as an extension to the core *CONSORT 2010 (Consolidated Standards of Reporting Trials)* and *SPIRIT 2013* (*Standard Protocol Items: Recommendations for Interventional Trials)* to guide the reporting of RCTs that underwent significant protocol amendments due to extenuating circumstances[47]. Unless extenuating circumstances apply, researchers conducting efficacy RCTs should determine and maintain the required sample size before the study initiation. However, trialists may fail to correctly estimate an *a priori* sample size due to a paucity of related research, leading to an insignificant treatment effect[14,18]. Patient burden is also high in efficacy RCTs due to comprehensive study protocols that may increase attrition[14]. This may be amplified in clinical populations already experiencing disease- and treatment-related side effects[48]. For example, patients with cancer frequently encounter issues with vein access, which can make obtaining blood samples for research purposes a considerable challenge. Patients may need to travel to research facilities for study visits, undergo additional measurements, and/or change their habitual dietary patterns during trial participation. Therefore, efficacy RCTs may hinder valid findings and successful implementation and scaling of nutritional interventions.

The Impact of COVID-19 on Nutrition Research

The COVID-19 pandemic introduced numerous challenges for efficacy RCTs. Many non-essential research activities were halted to prioritize patient and research staff safety[49–51]. Consequently, efficacy RCTs impacted by public health and safety measures faced one or more of the following: mandatory study cancelation, delayed in-person study visits, early termination due to low recruitment rate, increased attrition rate, limited funding support, incomplete outcome data collection and dissemination[49–51]. These factors are likely to result in missing outcome data, affecting study validity and the strength of future meta-analyses used to inform clinical guidelines[52]. Additionally, patients may have experienced changes to habitual dietary and physical activity patterns, and mental and/or physical health, all of which can impact ongoing trials[53]. The disruption to research during COVID-19 will likely have a long-term effect on knowledge mobilization, although the effects are yet to be fully elucidated. Such challenges emphasize the need for improved research processes and alternative trial designs to overcome the pitfalls of efficacy RCTs.

Conversely, the COVID-19 pandemic unexpectedly prompted improvements in overall research processes. Long-standing methodological issues, including challenges with research ethics board and/or regulatory approvals, and patient recruitment and enrollment, became more evident during the pandemic[54]. As a result, researchers and funding agencies prioritized high-quality research that could be conducted in a timely and cost-effective manner. This shift led to enhanced approval processes, including options for remote patient recruitment and electronic consent[55–57]. Research design and processes also evolved to incorporate technology-delivered interventions, monitoring, data collection, and dissemination of findings[58]. Improved Internet access or telehealth services billing processes were rapidly implemented, allowing underserved populations—those living in rural communities and older adults—to participate in research[59,60].

Adaptive Trials: Definition and Main Characteristics

Adaptive trials allow for pre-planned methodological modifications based on ongoing data collection without compromising the validity or integrity of results[28,30,61]. The adaptive design is particularly relevant when uncertainties arise during trial planning (e.g., ideal target population; duration and/or intensity of intervention)[61]. Trial modifications are not arbitrary; they are carefully considered before study initiation and guided by pre-defined, data-based criteria.

Examples of trial adaptations include sample size recalculation; broadening eligibility criteria to include patients most likely to benefit from the intervention; dropping an ineffective study arm; escalating treatment dose; comparing multiple treatment arms with a control arm over multiple stages; and early termination based on efficacy, futility, or safety results[28,30,61] (**Figure 2**). Another common adaptive strategy employs the Bayesian method, allowing researchers to select pre-planned adaptations based on predictions of follow-up parameter distribution and probability of trial success[62]. Researchers can opt to use one or more adaptive strategies although predetermined interim analyses—preliminary statistical analyses or review of data prior to trial completion—are recommended[28].

Documenting and sharing general information with the public, such as continuation or early termination of dose groups, is unlikely to bias trial continuation[63]. However, to support decision transparency and ensure interim analyses results are unbiased, adaptation details, including statistical decision rules and probability thresholds, should be made available upon trial completion[63]. Researchers may keep critical details of adaptations confidential while the study is ongoing to avoid operational bias[28,63]. The *ACE (Adaptive designs CONSORT Extension)* statement provides standards for publishing adaptive trials to ensure transparency[28].

Pragmatic Trials: Definition and Main Characteristics

Pragmatic trials evaluate the effectiveness of therapeutic interventions in real-world settings, or where they would be implemented, if successful[12]. Typically embedded within clinical settings, pragmatic trials often compare outcome measures between intervention group(s) and standard of care[10] (**Figure 3**). Pragmatic trials select a patient-oriented primary outcome that is relevant to and/or informed by patients[12]. Their eligibility criteria reflect the patient population that would receive the intervention in standard of care, enhancing generalizability[12]. Due to diverse patient populations, larger sample sizes are required to control for confounders and maintain statistical power, compared to efficacy RCTs[64]. In pragmatic trials, all patients are included irrespective of their adhere to the intervention, as the primary data analysis method is intention-to-treat analysis[12]. Furthermore, methodological aspects such as recruitment, research setting, care delivery, and follow-up seek to replicate real-world settings or standard of care. Pragmatic trials may be more feasible than efficacy RCTs and can accelerate knowledge translation into clinical settings[10,12,65].

The modified *PRECIS-2* (*Pragmatic Explanatory Continuum Indicator Summary)* is recommended for designing pragmatic trials aligning with patients' needs and for gauging the level of pragmatism across nine domains related to participant and investigator recruitment, intervention implementation, and outcome definition and analysis[12]. This tool enables researchers to evaluate the alignment of their proposed design with the trial's objectives[12]. Moreover, an extension of the standard *CONSORT* statement encourages adequate and standardized reporting of pragmatic trials, allowing knowledge users to evaluate the applicability of interventions in specific clinical practice areas[33].

Advantages of Using Adaptive and Pragmatic Trials in Clinical Nutrition Research

Adaptive trials incorporate methodological components that can advance clinical nutrition research (**Figures 2 and 3**). A significant advantage of these trials is the flexibility in tailoring intervention to patients' nutritional needs. Adaptive trials with multiple intervention arms can test different doses or composition of food and/or supplements, with interim analyses determining whether treatment arms are included or dropped for the remainder of the study[13,30]. This strategy helps establish the optimal dose and composition of food and/or supplements for the desired outcome[66]. Adaptive trial interventions can be extended to evaluate both short- and long-term responses if the interim analysis results are promising[28], enabling researchers to identify an optimal treatment time frame that achieves intended effects[30]. Many RCTs fail to identify intervention efficacy because the trial duration is insufficient to observe a marked physiological response to outcomes, or is shorter than the underlying disease treatment (e.g., chemo(radio)therapy cancer treatment)[67].

Adaptive design optimizes patient recruitment and enrollment. Interim sample size reassessment allows for modifications of the required number of patients to achieve appropriate statistical power[28] based on data-driven standard deviations of the primary end-point[68], conditional power analysis[69], and other approaches[70]. This is important in clinical populations with limited evidence of nutritional interventions or when earlier studies had heterogeneous populations, designs, and outcomes assessments, as these factors can contribute to an incorrect *a priori* sample size calculations for downstream trials[18,28]. Adaptive design may also be more ethical than efficacy RCTs as individuals most likely to benefit from the intervention are enrolled after the interim analysis, which is relevant for clinical populations already experiencing disease and treatment burden.

Increased acceptance and use of pragmatic trials can advance clinical nutrition research. These trials are generally embedded within clinical practice allowing patients' needs to be routinely assessed, monitored, and evaluated. Integration of researchers, patients, and care teams within the practice setting further facilitates optimization of individual nutritional targets[13]. Patients are also followed by their standard of care team to monitor disease progression, enabling adjustment of follow-up assessments to be extended beyond the duration of the intervention. Patient partners and other stakeholders, such as healthcare professionals and hospital managers, are often engaged throughout the research lifecycle, advising on trial aspects and producing meaningful findings[71]. Co-designing trials leads to more acceptable research processes and elicits positive emotions in stakeholders (e.g., confidence, pride), strengthening the bonds between researchers and communities[72]. While not unique to pragmatic trials, the use of electronic health records is common in these trials and enables rapid eligibility screening and the option for a virtual electronic informed-consent process[73]. Electronic health records can also facilitate data collection on healthcare resource utilization and cost-effectiveness analyses. The latter may reduce economic burden in the healthcare system by ensuring implementation of cost-effective interventions. Lastly, broad inclusion criteria promote eligibility and implementation of trials into clinical practice[30,65].

Adaptive and pragmatic approaches can improve trial design and promote patient-oriented research and patient-centered care in clinical nutrition. These trials can produce research findings that address patients' unique nutritional needs and reduce patient and healthcare system burden. Recruitment strategies also minimize the likelihood of trial failure due to unsatisfactory enrollment. These factors together may help accelerate the translation of nutrition-focused trial findings to clinical practice and scale-up of interventions to broader practice settings.

Examples of Adaptive and Pragmatic Trials in Nutrition Research

A Medline search conducted up to February 04, 2023 using a combination of keywords related to nutritional interventions (“nutritional therapy”, “diet”, “dietary supplements”) and adaptive or pragmatic trials resulted in 106 records. Among these, 16 nutrition studies employed an adaptive design, and 40 studies utilized a pragmatic design. This search strategy focused on alternative design trials that used the terms “adaptive” or “pragmatic” in their title, abstract, subject heading, and/or author keywords. **Table 2** describes selected examples of nutrition-related adaptive and pragmatic trials. The adaptive trials discussed herein implemented various methodological modifications based on study objectives, while the included pragmatic trials shared similar aspects of trial design.

Challenges Conducting Adaptive and Pragmatic Trials in Clinical Nutrition Research

Adaptive and pragmatic nutrition trials are challenging to plan, implement, and analyze. Compared to efficacy RCTs, these trial designs require additional expertise and time for developing and implementing study protocols[61,80,81]. For example, obtaining ethics and regulatory approvals may take longer for alternative trials than for efficacy RCTs. While the pandemic has led to streamlined processes, it remains unclear whether these improvements extend to alternative trials. This presents a particular challenge for multicenter trials, where numerous study sites are involved in the approval process, and ethics board reviewers may have limited familiarity with alternative designs.

Challenges that are more relevant but not limited to pragmatic trials include the time needed for engaging with stakeholders and training clinical staff. The time commitment ensures recruitment rates are feasible and achieved, nutritional interventions are implemented into routine practice, and data are collected per the study protocol (i.e., fidelity)[80]. The need for adequate staffing is also a concern, given the additional time required for study visits, administering the intervention, and assessing study-specific outcomes, particularly in under-resourced settings and in the COVID-19 aftermath[80]. For instance, in United States cancer centers, the ratio of registered dietitian nutritionist to patients with cancer was 1:2,308, with each dietitian evaluating seven patients daily[82]. Insufficient physical infrastructure (e.g., additional clinical space) may also hinder trial implementation.

Outpatient pragmatic trials may struggle to measure dietary intake, control participant's usual diets, or evaluate nutrition-related outcomes. Although self-reported dietary data offers valuable insight into food intake and dietary patterns, there are inherent limitations[83]. For example, misreporting dietary intake is prevalent across assessment tools, body mass index categories, and age groups[83]. Body composition, a common outcome in nutrition trials, can also be difficult to evaluate due to the limited availability of infrastructure or trained personnel for routine assessment[84]. If body composition techniques are inaccessible, surrogate markers of muscle mass (calf or mid-arm circumferences) or fat mass (waist circumference, skinfolds, and body mass index) may be considered[85]. However, surrogate makers lack sensitivity and specificity compared to gold-standard methods and may not accurately reflect the treatment effects of nutritional interventions[46], as these effects are often smaller than those of drug treatments. Concerning health record data acquisition, extracting outcome measures can be difficult due to fragmented or complex electronic systems, or the continued use of paper charts.

Treatment contamination in nutrition research challenges alternative designs, particularly pragmatic trials with less restrictive protocols[14,65]. In such trials, patients who do not receive the initial intervention they were randomized to, including those from the control group who inadvertently receive the intervention, experience treatment contamination. Factors contributing to study arm contamination include changes in standard care practices during the trial; limited dietitian availability for delivering interventions in a clinical setting; controls requiring more intensive nutritional therapies that resemble the study intervention; and controls changing eating patterns once introduced to the study or in an effort to improve nutrition-related symptoms (e.g., secondary to anti-cancer treatment). Contamination across study arms can diminish outcome differences in intention-to-treat analysis, potentially leading to failed trials[86]. Statistical approaches to address treatment contamination are discussed elsewhere[86].

Analyzing and interpreting adaptive and pragmatic trial data can also be difficult. Consulting a statistician during trial planning can help avoid biases in data distribution, treatment effects, confidence intervals, and *p* values[30]. For example, cluster randomization is a common approach used in pragmatic trials that may yield misleading statistical analysis[37,87]. In cluster randomized trials, groups of patients with similar characteristics—rather than individuals—are randomized to the intervention; however, these trials often fail to account for correlation between individuals in the same cluster, with statistical analysis conducted at the cluster level instead, compromising findings[37]. These and other issues, along with possible mitigations, are discussed elsewhere[30,37]. Ultimately, early statistical planning is essential for accurate extrapolation of trial results to clinical practice.

Practical Considerations for Adaptive and Pragmatic Clinical Nutrition Trials

Figures 4 and **5** illustrate practical considerations for conducting adaptive and pragmatic nutrition trials. Substantial effort is required during the planning stage, and appropriate execution and data analysis are crucial for study success and the integration of nutritional interventions into clinical care settings.

Perspectives in Adaptive and Pragmatic Nutrition Trials

Continued efforts in disseminating information that educates users about the diverse aspects of adaptive and pragmatic trials are required to enhance their application in clinical nutrition research[80,81]. Training should be provided to researchers across all career stages (including trainees), members of ethical and regulatory committees, industry partners, funding agencies, and other stakeholders to expedite planning, funding, approval processes, and delivery of evidence-based results. This training would promote sound planning of alternative nutrition trials, resulting in higher quality evidence. For example, researchers should strive to simplify trial assessments, evaluate patient-oriented outcomes, and engage stakeholders[71,88,89]. Intervention flexibility should also be considered early, particularly when intervention adjustments are based on patient's emerging needs (e.g., changes in prognosis)[89].

Several strategies should be explored to enhance research processes in adaptive and pragmatic nutrition trials. For instance, a centralized ethics review could expedite multi-center study initiation and alleviate administrative delays[88]. Automated patient screening through electronic health records and electronic, waived, or modified (e.g., verbal) informed consent, could reduce staff workload related to patient recruitment. Recruitment simulation is a tactic that could widen eligibility criteria and improve recruitment and retention[88]. Since blinding patients is rare in nutrition trials, approaches to minimize detection bias should include selecting objective outcomes or blinding outcome assessors[88]. Researchers ought to evaluate facilities' readiness to implement nutritional interventions into routine care, a vital factor for pragmatic trial success[89]. Lastly, research funding calls emphasizing alternative trial designs in nutrition research are necessary to propel this research field forward[88].

Adaptive and Pragmatic Nutrition Trials in Oncology

Cancer is one of the many clinical conditions that benefit from targeted nutritional care and multimodal approaches for management and optimization of patient outcomes. Although guidelines addressing the nutrition care process for patients with cancer exist, discrepancies in intervention recommendations persist[25,26,90,91]. This heterogeneity is partly due to limited evidence on nutritional intervention effects, especially during cancer treatment, resulting in recommendations primarily based on expert opinions[92,93]. Only three of 43 (7.0%) recommendations in the European Society for Clinical Nutrition and Metabolism guidelines on nutrition in cancer were concurrently rated as a high level of evidence and strong level of recommendation[25]. The American Society of Clinical Oncology proposed only two recommendations for nutritional interventions in patients with advanced cancer and cachexia[90]. Although evidence was from RCTs with at least 20 patients, both recommendations were rated as moderate strength of either low evidence quality or based on informal consensus. Also, patients' nutritional needs vary depending on tumor type, disease stage, treatment modality, and nutrition impact symptoms[94], adding to the challenges in nutrition research and clinical practice recommendations. Thus, high-quality trials that address the unique nutritional needs of patients with cancer are needed.

Evidence-based recommendations might be limited by insufficient funding for nutritional interventions in cancer. Nutrition research at the United State National Cancer Institute has received less grant funding than other cancer-related areas, with a 44% decline in funded research between 2012−2018 and a decrease in financed clinical trials over the last decades[95]. Most grant applications have focused on mechanisms and dietary supplementation rather than on dietary patterns, and were rarely submitted by dietitians as principal investigators[95]. By providing additional funding opportunities, nutrition research can be advanced, supporting evidence-based nutritional recommendations in oncology. Adaptive and pragmatic trials offer promising alternatives to efficacy RCTs in oncology nutrition research (**Figure 6**) and have been discussed as strategies to advance the field at the *Pathways to Prevention* workshop, organized by the National Institutes of Health[93].

Adaptive designs in oncology nutrition can address trial planning uncertainties and target patients' nutritional needs, without further compromising their health or substantially increasing the burden of research participation. This approach can be achieved by testing different doses or compositions of food and/or supplements and stopping the trial early if concerns about safety, efficacy, or futility arise. Adaptations to nutritional interventions should be based on treatment cycles due to suboptimal nutrition intake and low adherence to nutritional interventions during chemotherapy[67]. Nutrition impact symptoms including nausea, anorexia, and mucositis affect patients' appetite and ability to eat or digest food; thus, tailoring interventions to these symptoms may improve nutritional care, nutritional status, and health outcomes in addition to reducing treatment-related toxicities[96]. For example, interventions enhancing acceptability of foods with complex textures can be provided to patients experiencing dysphagia, and nutritional counseling aimed at increasing energy-dense foods can be offered to patients losing weight[96].

Pragmatic trials can help minimize patient burden during trial participation[97]. Study assessments are typically conducted during follow-up visits with healthcare professionals, eliminating the need for additional visits beyond standard of care. Capturing laboratory information from the electronic medical record may mitigate the need for additional research blood draws in patients with challenging vein access. Pragmatic trials include outcomes relevant to patients with cancer (e.g., quality of life, physical function) and stakeholders (e.g., cost-effectiveness analysis). Additionally, pragmatic trials' broader eligibility criteria make their findings generalizable to more patients receiving care[97]. This ensures equal access to trials and nutritional care for older or less fit patients, who are often excluded from oncology trials[98]. Pragmatic trials may be appealing to dietitians, as they can be involved in research while providing patient care; however, this might not be feasible in cancer centers with a shortage of nutritional care staff[82]. Currently, only a few dietitians hold doctoral degrees, apply for, and receive funding for oncology nutrition research[95]. As pragmatic trials in nutrition are carried out, this situation may evolve.

When conducting alternative trials in oncology nutrition (**Figure 6**), researchers may face additional challenges beyond those already discussed. Issues such as treatment discontinuation, shifting from a curative to palliative intent, loss to follow-up, and poor adherence or compliance to interventions are common in this patient population[97]. During trial design and data analysis, statistical approaches accounting for missing data must be discussed and implemented to minimize treatment efficacy or effectiveness bias. Blinding can be challenging, and an un-blinded approach might affect clinician-reported outcomes (e.g., treatment delays, dose-reductions) and patient-reported outcomes (e.g., quality of life)[97]. Low accrual rate is another common obstacle in oncology nutrition trials[99].

The REthinking Clinical Trials (REaCT) Program[100] was developed to address these barriers in oncology clinical trials through pragmatic research. As the largest initiative of its kind in Canada, it has conducted over 20 trials to date[100]. The REaCT program employs pragmatic trial design and the implementation of commonly used cancer therapies. Additionally, it conducts surveys with stakeholders to define research questions and performs cost-effectiveness analysis to evaluate interventions' economic impact[100]. The REaCT program serves as a model for advancing the use of alternative designs in oncology nutrition research and other chronic conditions.

Conclusions

Well-planned adaptive and pragmatic nutrition trials hold the potential to generate high-quality evidence, enhance generalizability, and expedite the implementation of interventions into patient care. By employing these trials, the availability of evidence-based nutritional recommendations that address both efficacy-effectiveness and evidence-practice gaps can be accelerated. While there are limitations, adaptive and pragmatic trials should be considered as valuable approaches to clinical nutrition research. Rather than dismissing efficacy RCTs, which are feasible and appropriate for answering certain research questions, we encourage nutrition researchers to recognize their limitations and consider alternative trial designs, where appropriate (**Figure 1**). Continuous effort in training nutrition researchers and health research stakeholders on alternative designs is crucial for promoting the appropriate use of adaptive and pragmatic nutrition trials.

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Author Contribution Statement

CEO and CMP designed research; CEO and KLF conducted literature search; CEO, KLF, and CMP contributed to writing—original draft preparation; CEO, KLF, NK, EBT, CKS, JHR, and CMP contributed to writing—review and editing. All authors have read and approved the final manuscript.

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Ethical Approval

Not applicable because this is review article and it does not include research with human or animal subjects.

Competing Interests

CEO has received honoraria from Abbott Nutrition. CMP has previously received honoraria and/or paid consultancy from Abbott Nutrition, Nutricia, Nestlé Health Science, Fresenius Kabi, AMRA Medical, and Pfizer. NK has received honoraria and/or paid consultancy from Abbott Australasia. KLF, EBT, CKS, JHR – no conflicts of interest.

Figure Legends

Figure 1. Traditional and alternative potential approaches to clinical nutrition research.

Research questions often stem from clinical observations and are typically tested initially through observational studies, notably retrospective cohort studies. These studies establish associations rather than causality, thereby generating hypotheses. Depending on the research question, these hypotheses can be further tested through pre-clinical studies (including cell and animal studies) or small human non-randomized pilot trials, assessing safety, dosage, and providing preliminary data for future larger studies. Nutritional interventions are subsequently evaluated using randomized controlled trials (RCT), which can be divided into two types: efficacy and effectiveness RCTs. When suitable, well-designed adaptive and pragmatic trials can replace non-RCTs and efficacy trials, optimizing clinical nutrition research.

Figure 2. Adaptive trial modifications and advantages in the field of clinical nutrition research.

Figure 3. Features of pragmatic trials and their advantages in clinical nutrition research.

Figure 4. Key elements to consider when planning, executing, and analyzing adaptive trials in clinical nutrition. *ACE, *Adaptive designs Consolidated Standards of Reporting Trials (CONSORT) Extension*, (available at https://doi.org/10.1186/s13063-020-04334-x[28]).

Figure 5. Key elements for researchers to consider when planning, executing, and analyzing pragmatic nutrition trials. *PRECIS-2, *PRagmatic Explanatory Continuum Indicator Summary*

(available at https://doi.org/10.1136/bmj.h2147[12]*)*; †CONSORT Extension, *Consolidated Standards of Reporting Trials Extension (*available at https://doi.org/10.1136/bmj.a2390[33]).

Figure 6. Advantages and challenges of conducting adaptive and pragmatic trials in oncology nutrition research.