

Table 1. Advantages and disadvantages of efficacy randomized controlled trials and alternative (adaptive and pragmatic) trials in the context of clinical nutrition research.

Domain	Efficacy trials	Alternative trials
Trial objectives	 • Evaluate an intervention in a controlled environment.	 • Enhanced assessment of intervention efficacy in adaptive trials, or effectiveness in pragmatic trials.
Design flexibility	 • Fixed and strict intervention protocols. • Lacks flexibility for extenuating circumstances.	 • Flexibility in design elements and tailoring interventions to patients' nutritional needs. • Flexibility during extenuating circumstances.
Double-blinded design	 • Commonly used in nutritional supplementation trials.  • Can be challenging in other nutritional interventions.	 • Possible in nutritional supplementation trials (adaptive trials).  • Can be challenging in other nutritional interventions and pragmatic trials.
Eligibility criteria	 • Restrictive; limits recruitment and generalizability of findings.	 • Can be modified in adaptive trials or can include a more diverse

Domain	Efficacy trials	Alternative trials
	• Enrollment of patients most likely to respond positively and/or adhere to nutritional interventions.	patient population in pragmatic trials; optimizes patient recruitment and enrollment. • Enrollment of patients independent of responsiveness, comorbidities, or history of adherence.
Confounding factors (e.g., comorbidities, medication use, habitual dietary patterns, malabsorption disorders)	 • Less likely to produce bias.	 • Less likely to produce bias in adaptive trials.  • Challenging to control for in pragmatic trials.
Treatment contamination	 • Unlikely to occur across study arms.	 • Can occur across study arms.
Control groups	 • Restrictive protocols.	 • Standard of care is often used.

Domain	Efficacy trials	Alternative trials
Outcome assessment	 • Use of precise and valid techniques to minimize measurement errors.	 • Use of precise and valid techniques to minimize measurement errors in research settings.  • Such techniques are rarely available in clinical settings.
Follow-up (i.e., responses to nutritional interventions)	 • Usually tested in the short term, which may not be long enough to observe a marked physiological response.	 • Can be more easily assessed in the short and long term.
Time, expertise, infrastructure, and costs	 • Required time and expertise for developing and implementing study protocols. • Costly and complex infrastructure for trial execution.	 • Requires additional time and expertise for developing and implementing study protocols. • Trials require less complex infrastructure and, depending on the design, costs may be lower.

Domain	Efficacy trials	Alternative trials
Patient and healthcare system burden	 • Burdensome due to comprehensive study protocols.	 • Reduced burden.
Statistical analysis	 • Intention-to-treat analysis is the norm.  • Per protocol analysis is also often conducted to evaluate intervention efficacy under ideal adherence conditions.	 • Intention-to-treat analysis is the norm.  • Statistical analysis and interpretation can be more challenging.
Ethics review and approval	 • Faster as ethics board reviewers are more familiarized with efficacy trials.	 • Can take longer due to reviewers' unfamiliarity with trial design, trial complexity, and multicenter approvals.
Stakeholder involvement	 • May be possible throughout the trial life cycle.  • Less likely than in alternative trials.	 • Can enhance trial impact and expedite its implementation.  • Additional time needed.
Real-world applicability	 • Controlled feeding studies can yield robust results.	 • Interventions are tailored to patient's needs and can be embedded within patient

Domain	Efficacy trials	Alternative trials
	 - Controlled feeding studies are less likely to be applicable in real-world settings. - Evidence from a single study is rarely translated into clinical practice.	care, expediting the implementation of findings. Increased likelihood of trial intervention and findings being integrated in patient nutritional standards of care and scaled-up to additional practice settings.

 Advantages;  disadvantages.