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Optimal Design of Clinical Trials of Dietary Interventions in Disorders of Gut-Brain Interaction

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There is accumulating evidence for the fundamental role of diet in the integrated care of disorders of gut-brain interaction. Food is a complex mixture of components with individual, synergistic, and antagonistic effects, compared with the relative purity of a pharmaceutical. Food is also an inherent part of individuals' daily lives, and food choice is strongly tied to food preferences, personal beliefs, cultural and religious practices, and economic status, which can influence its ability to function as a therapeutic intervention. Hence, randomized controlled trials of dietary interventions carry unique methodological complexities that are not applicable to pharmaceutical trials that if disregarded can pose significant risk to trial quality. The challenges of designing and delivering the dietary intervention depend on the type of intervention (i.e., nutrient vs food supplementation or whole-diet intervention). Furthermore, there are multiple modes of delivery of dietary interventions, each with their own advantages (e.g., the high precision of feeding trials and the strong clinical applicability of dietary counseling trials). Randomized placebo-controlled trials of dietary interventions are possible with sufficient attention to their design and methodological nuances. Collaboration with experts in nutrition and dietetics is essential for the planning phase; however, even with expert input, not all challenges can be overcome. Researchers undertaking future dietary trials must be transparent in reporting these challenges and approaches for overcoming them. This review aims to provide guiding principles and recommendations for addressing these challenges to facilitate the conduct and reporting of high-quality trials that inform and improve clinical practice.

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INTRODUCTION

There is rapidly accumulating evidence for the importance of diet in the integrated care of disorders of gut-brain interaction (DGBI). Although there is substantial guidance from regulatory bodies for the design and reporting of pharmacological trials, there is no such guidance for dietary intervention trials, which are characterized by many unique complexities that if not properly accounted for can pose risks to trial quality and interpretation.

Drugs invariably contain a highly purified chemical compound given in a precise dose and formulated to increase the likelihood of delivery to the desired region of the gastrointestinal (GI) tract. Decisions on dose, frequency, and timing of administration are informed by pharmacodynamic, pharmacokinetic, and basic toxicity studies. These observations regarding drug delivery are in contrast to studies addressing the efficacy of diet as an intervention. Food is a complex amalgam of components with individual, synergistic, and antagonistic effects on the luminal microenvironment. The types and doses of nutrients and chemicals within food are also more variable than would be tolerated in a pharmaceutical. There are unique trial design challenges that come with dietary trials. In particular, how the diet intervention is delivered to study participants and the choice of comparator and blinding can all introduce bias that can reduce confidence in the results.

Given the rapidly progressing evidence for diet in the treatment of DGBI, an update of previous guidelines (1) is warranted. This review will define and describe the various types of dietary interventions and their mode of delivery, discuss the design and methodological complexities specific to dietary trials, provide new advice for measuring patient-centered end points, and provide recommendations for researchers to address these challenges to conduct methodologically rigorous, high-quality trials that can inform and improve clinical practice.

Dietary intervention trials

Dietary interventions can involve supplementation with nutrients ("nutrient supplementation") or foods ("food supplementation"), changes in whole diet ("whole diet intervention"), or restriction and rechallenge of specific dietary components (Table 1). Trials of restriction and rechallenge come with unique challenges (e.g., nocebo and physiological responses to nonfood challenges) that are described in detail elsewhere (1). For the purposes of this review, all classes of interventions will be referred to as "dietary interventions." The mode of delivery of dietary intervention will affect the challenges and strengths and limitations faced.

Modes of delivery of dietary intervention

Dietary interventions with foods or whole diets can be delivered either through direct feeding or dietary counseling or a hybrid of

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Table 1. Description and examples of different dietary intervention trials

	Type of intervention	Example
Nutrient supplementation	Consumption of a specific nutrient(s) by a capsule, sachet, or solution delivery system	Isolated fiber intervention in IBS (2) Mixed fiber intervention in IBS (3)
Food supplementation	Addition of a single food	Kiwifruit supplementation in constipation (4) Prune supplementation in constipation (5)
Whole-diet intervention	Altered food intake across multiple food groups often personalized according to an individual's food preferences	Low FODMAP diet in IBS (6) Low salicylate diet in IBS (7)
Individualized whole-diet intervention	The nature of the whole-diet intervention is different for different people	IgG-based exclusion diet in IBS (8) Endomicroscopy-based exclusion diet in IBS (9)
Restriction and rechallenge	Restriction then reintroduction of specific foods or food components, reminiscent of the gold standard method of identifying adverse food reactions Components are introduced in pure form (e.g., powder, liquid, and capsule) or by supplementing with the relevant food(s) with inevitable differences in blinding Termed "elimination-rechallenge" in cases where there are undetectable quantities of the food component of interest in the diet (e.g., gluten)	FODMAPs in IBS (10,11) Gluten in IBS (12)

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, Irritable Bowel Syndrome.

the 2, and there are advantages and disadvantages for each (Figure 1). Feeding trials involve provision of all food (and sometimes beverages) to participants for the duration of the intervention. Diets are carefully designed to alter only the dietary component(s) of interest while nutritionally matching all other aspects with the control group. Feeding trials can be performed either as a domiciled feeding trial, where participants reside at the research facility and researchers supply all dietary intake and measure outcomes (13), or in the free-living context, where meals are prepared in bulk and delivered fresh or frozen to participants. Hybrid feeding trials are also possible, whereby some meals (usually during working hours) are consumed at the research unit and the remainder (usually evening and weekends) are consumed at home (14). Web-based or mobile applications, while mostly used as an adjunct to dietary counseling, may also be used as the sole delivery method for whole diet interventions (15). Although trials are scarce, if these methods are shown to be safe and efficacious, this could enable widespread clinical use.

There are many major advantages of feeding trials including high adherence and the ability to design a bespoke placebo diet; however, feeding trials have several disadvantages (Figure 1). They are expensive, and external validity can be limited due to the inherent absence of challenges that

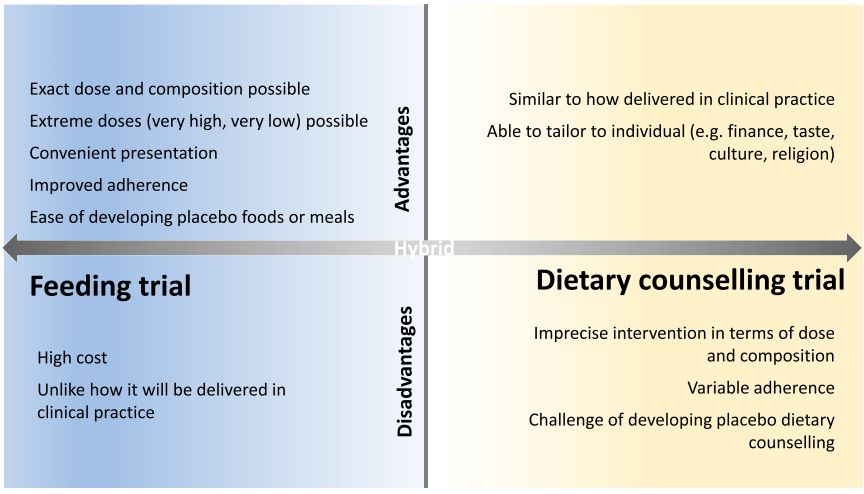

Figure 1. Advantages and disadvantages of delivering a dietary intervention as a feeding or dietary counseling trial. Feeding trials offer high precision in delivery of the intervention but are usually intensive and costly, whereas dietary counseling trials have greater external validity because they better resemble how an intervention is delivered in practice, although developing placebo dietary counseling is challenging. Hybrid models that combine feeding and dietary counseling are also used, whereby some foods/meals are provided and ad libitum intake is adjusted through dietary counseling.

jeopardize adherence when the dietary intervention is used in real life (e.g., participant motivation and understanding of advice provided).

Dietary counseling is the most common method of diet delivery in DGBI dietary trials and is highly applicable to the clinical setting. Participants are counseled as to the foods to include and/or restrict, and written resources are often provided. Counseling should be performed by a specialist gastroenterology dietitian who has the expertise to personalize the diet based on personal requirements (e.g., food preferences, cultural and religious practices, and socioeconomic restrictions) while ensuring nutritional adequacy. Explanation of the physiological effects of a diet may be provided in unblinded trials. There is inevitable imprecision in the intervention because each participant will follow a different diet and adhere to the intervention to differing degrees (Figure 1). Other dietary education modalities are also available, including group counseling (16,17), instruction provided through written text (e.g., books and online resources) or mobile applications. Education through a mobile application may be effective at improving symptoms (18), but evidence of optimal education strategies, or combinations of these, is limited.

Design and methodological issues and recommendations for dietary trials

RCTs are the gold standard for determining the efficacy of a dietary intervention. Dietary RCTs can be designed as a parallel or crossover trial. Crossover trials require fewer participants but are more influenced by dropouts, and the minimum washout duration is often unclear. Run-in periods are sometimes used before randomization to homogenize or optimize background diet or to allow for adaptation (e.g., to high-fiber diet). Run-in periods should not be used generally as a method to select highly adherent participants because this leads to a highly selected population with limited real-world translation; however, this may be useful for feeding trials that are not designed to be pragmatic and in which minimizing attrition reduces the cost of running the trial. Regarding clinical end points, investigators should be encouraged to use high-quality, clinically or physiologically relevant, and validated end points from the literature.

There are additional methodological considerations for dietary trials, specifically in DGBI. In particular, trials including microbiome end points must consider the rapidity of diet-induced microbiome changes and the length of time required for diet-induced microbiome changes to stabilize in a new state of ecological homeostasis (19,20), the substantial temporal intra-individual variability in microbiome composition and function (21), and the potential confounding imparted by medication and comorbid conditions (22,23). A comprehensive summary of methodological issues relating to diet-microbiome research is provided elsewhere (24). Furthermore, just as pharmacokinetics inform design of pharmaceutical studies, assessment of physiological responses to diet relevant in DGBI, such as transit time and fermentation, should occur in consideration of the temporal effect of diet and the sampling conditions (e.g., fed or fasted state, habitual diet, and caloric content).

Biases in dietary trials

Biases in RCTs can be participant-derived or investigator-derived (Figure 2). Selection bias can alter baseline participant characteristics and subsequently interfere with accurate interpretation of clinical effects (25). For example, participants in a fiber supplementation trial with optimal habitual fiber intake may have differential responses to those with suboptimal fiber intake (26). Recruitment strategies that target individuals with a wide range of dietary habits and the use of a neutral language to mask the study hypothesis can help to mitigate selection bias.

The Hawthorne effect (modification of behavior in response to being observed) is common in both dietary trials and in DGBI. Both this and response bias can reduce accuracy of the dietary assessment, which can lead to underestimating energy and total fat intake (27). Strategies to reduce the impact of these biases are discussed below. Compliance bias can pose a considerable challenge during the intervention phase. Preexisting diet beliefs and behaviors can substantially influence an individual's ability to comply in dietary trials. A myriad of factors affect these behaviors including cultural background and ethical and religious beliefs (28), the high prevalence of perceived diet-symptom associations (29,30), and disordered eating (e.g., orthorexia nervosa and avoidant restrictive food intake disorder) (31) in DGBI. Excluding participants with disordered eating patterns may reduce the impact of this type of bias and mitigate safety concerns, particularly for whole-diet intervention trials.

Finally, expectations regarding the therapeutic potential of a food or diet based on prior knowledge can shape clinical responses to the dietary intervention or placebo and lead to participant expectancy effects. The increasing accessibility to diet information through lay media or the scientific community has facilitated widespread self-directed dietary experimentation, particularly in irritable bowel syndrome (IBS) (32), which could reduce or exaggerate response among participants. In whole-diet counseling trials, it may be necessary to include only intervention-naïve participants and/or to restrict information regarding the nature of the intervention where it is ethical and practical to do so.

Intervention and placebo design and delivery

Precision of the intervention. An inherent challenge of dietary trials is that excellent precision is not universally possible. The exact dose and composition of the intervention is not always known or able to be applied consistently across participants. Precision is influenced by the mode of delivery, adherence, and the degree of dietary confounding (Table 2). For example, nutrient supplementation trials with high levels of intervention "purity" (i.e., known dose and composition) achieve high precision because adherence is usually very good and can be monitored with accuracy, and the intervention rarely affects background dietary intake. Food supplementation trials are more subject to dietary confounding because the supplemented foods can lead to homeostatic displacement of other food(s). For example, 2 kiwifruits provide up to 25% of the daily fiber requirements and will affect intake of other fruits and snacks. Thus, changing one component of the diet leads to compensatory changes in other components, a problem termed dietary collinearity. The precision of whole-diet trials is highly dependent on the mode of delivery. Whole-diet feeding trials allow quantification and compensation for collinearity. However, whole-diet counseling trials usually incorporate personalized advice, which leads to dietary changes that differ between participants with variable collinearity influences on background diet. This must be weighed against the high clinical applicability and relatively low cost of dietary counseling to deliver the intervention.

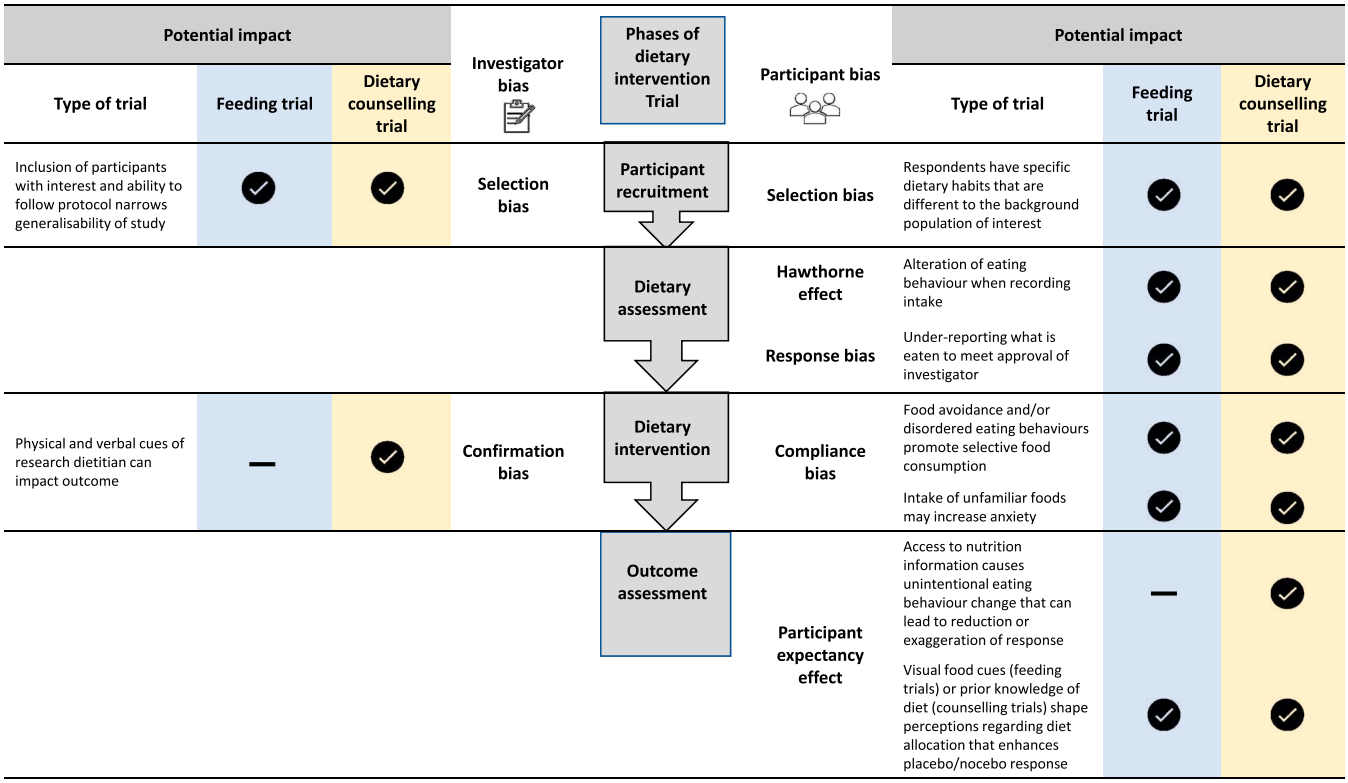

Figure 2. Potential for bias in dietary intervention trials. Some biases are unique to dietary intervention trials, and others are common to dietary, pharmaceutical, and behavioral trials. Tick icons indicate that the bias is present, and hyphens indicate that the bias is not present.

Controls and blinding. A unique complexity of dietary trials, and particularly whole-diet trials, is the selection and design of an optimal control. A host of options are available including habitual diet (inevitably unblinded) or "active" interventions such as an alternative diet or nondiet intervention. Placebo controls are, however, the gold standard choice because they facilitate treatment blinding. This is of extreme importance in DGBI for which end points are largely self-reported. Placebos are relatively straightforward to design in nutrient supplementation trials, and double blinding is easy to implement. However, incorporating a placebo control in food supplementation and whole-diet trials, in which the control must mimic the intervention to enable blinding but be inert, is more difficult (Table 2). The ease of designing a placebo control for a food depends on the nature of the component under investigation. This can be relatively easy (e.g., for caffeine, standard coffee vs decaffeinated coffee) or be complex and impossible (e.g., what makes a placebo for an apple?).

In whole-diet feeding trials, placebo controls can be delivered with high precision. Sham meals can be prepared to appear and taste similar to the intervention, and double blinding is possible because study meals can be double-coded by external staff before delivery (7,33). Implementing a placebo control for whole-diet counseling interventions is considerably more challenging (Table 2) and has been undertaken with varying degrees of rigor (8,34–37). A sham diet for this purpose must lead to similar complexities of dietary change but must not affect intake of nutrients or the food component of interest. Further criteria for sham diet design and testing are detailed elsewhere (38). The dietitian delivering the advice cannot be blinded (single-blind only); however, it is possible for the research team measuring outcomes to be blinded (double-blind). However, care must be taken to limit unblinding of the participants where interventions are accepted in practice (e.g., disguise the intervention in trial advertisements and only include participants who are diet-naïve).

In all cases, it is recommended that attempts to limit investigator bias where double blinding is not possible is described and that researchers collecting and assessing outcome data are blinded to participant allocation until analysis is final (39). The success of blinding should be measured (asking participants to guess their allocation at the end of the trial) and reported, although it can be influenced by whether the symptomatic response was achieved. Successful blinding might be indicated by high uncertainty about allocation or an equal distribution of correct and incorrect responses (40).

Powering and sample size calculation

Like all clinical trials in DGBI, dietary trials should be adequately powered to detect differences in the primary outcome and should be accompanied by a sample size calculation. However, the availability of data required to calculate a sample size (i.e., effect size estimates for intervention and placebo and variability) presents unique challenges.

First, owing to the paucity of trials, data for the effectiveness of an identical dietary intervention or identical placebo on the primary outcome may not be available, and where available, they may not be measured in the same study.

Second, variation in response to dietary intervention is notoriously high resulting in high SDs for sample size calculations.

Table 2. Factors to consider in the design and delivery of interventions and corresponding placebo for dietary interventions

Types of dietary interventions	Mode of delivery	Intervention design			Placebo design	
		Challenges for design and delivery		Overall precision	Challenges for design and delivery	Overall precision
		Dietary confounding[a]	Adherence			
Nutrient or nutraceutical supplement (e.g., vitamin D, probiotic, and fiber)	Feeding	Low	High	High	Usually easy to prepare a placebo of similar appearance and taste	High
Food intervention (e.g., rye bread and lactose-free milk)	Feeding	Probable	Variable	Moderate	Whole-food (e.g., specific fruit) placebo can be difficult to prepare to mimic appearance and taste of intervention Composite-food (e.g., specific bread or milk) placebo is usually possible to prepare with similar appearance and taste	Moderate
Whole-diet interventions (e.g., high-fiber diet and low FODMAP diet)	Feeding	Low	High	High	Usually possible to prepare placebo meals that are similar to intervention meals but includes/excludes the item of interest (e.g., sham-diet meals)	High
	Counseling	High. Impact on background diet varies between participants.	Variable	Low to moderate	The placebo (sham) diet should seem credible and affect background diet in similar ways as the intervention	Low to moderate
Individualized whole-diet interventions (e.g., IgG-based exclusion diet and endomicroscopy-based exclusion diet)	Feeding	Low	High	High	Usually possible to prepare placebo meals, but they must differ depending on the individualization (e.g., the placebo to a soy exclusion should contain soy)	High
	Counseling	High. Impact on background diet varies between participants and depends on the intervention.	Variable	Low to moderate	Very challenging to provide dietary counseling that includes/excludes the item of interest, and this will vary depending on individualization.	Low to moderate

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IgG, immunoglobulin G.
[a]Dietary confounding refers to the extent to which the dietary intervention also affects the intake of background diet. For example, a kiwifruit intervention may displace other snacks from the diet and a fiber intervention may increase satiety and reduce intake at mealtimes. Dietary confounding reduces the precision of the intervention because the dietary change that occurs is not simply the addition of the nutrient or food into the diet (i.e., kiwifruit or fiber) but also the change in intake or removal of other foods from the diet.

For example, some people respond completely, some moderately, and some not at all, which is governed by background diet, physiological variation in the mechanisms of action of the intervention, and variability in adherence.

Third, placebo and nocebo effects for dietary interventions are high due to strong beliefs about diet and the often-intensive clinician-patient interaction. Although the high placebo effect in dietary trials replicates what occurs in real life, in research, it requires the dietary intervention to achieve a very high level of success to demonstrate efficacy over placebo that might approach the ceiling of response rates.

Overall, unknown or inconsistent data for the effect size of a dietary intervention and wide variation in response, partnered with high placebo rates, can result in calculated sample sizes that are prohibitively high and might exceed the available funding to complete high-quality dietary trials.

Measuring dietary intake

Collection of dietary data enables objective evaluation of participant adherence in dietary trials. Adherence, at least in dietary counseling trials, can be influenced by skills of the dietary educator, participant understanding, health psychology, and financial and environmental access to foods. Adherence should ideally be determined by measuring intake of the dietary component of interest (e.g., fiber intake in g/d) rather than unvalidated arbitrary adherence measures (e.g., the threshold number of high-fiber foods consumed). Adequate adherence should be defined *a priori*. Dichotomous adherence ratings can be based on a specific threshold (e.g., 80% of nutrient/placebo supplements consumed (37) or 95% of study diet consumed (41)), for which there is no established gold standard or a statistically and nutritionally significant change in intake of the dietary component. Comprehensive dietary intake assessment also enables dietary confounding and nutritional

Table 3. Dietary assessment tools and their advantages and disadvantages

Dietary assessment method	Description	Output	Advantages	Disadvantages
Prospective				
Direct observation	In a feeding study, especially a domiciled feeding study, food consumption is calculated by subtracting left-over food from the food provided. Intake of nonsite meals is recorded.	Energy, fiber, macronutrients, micronutrients, additional food constituents depending on database access (e.g., FODMAPs and gluten) Food groups Number of meals	As precise as weighed food record	Consumption of food external to the trial is possible Relies on participant returning all remaining food/meals
Weighed food record	Participants weigh and record all food and beverages in real time Usual duration 3–7 d, including 1–2 weekend days	As for direct observation	Most precise measure of actual dietary intake Good agreement with biological dietary biomarkers	Very burdensome for participant Burdensome for researcher (participant training and data validation and analysis) May influence eating behavior Difficult to record meals not self-prepared May require assessment of interobserver agreement between coders
Unweighed food record	Participants record estimated quantities of food and beverages in real time Usual duration as for weighed food record Household measures and diagrams used to estimate weight	As for direct observation	Less burdensome for participant than weighed food record	Burdensome for researcher (participant training and data validation and analysis) May influence eating behavior Participants may underestimate or overestimate quantities
Retrospective				
24-hr recall	Food and fluid intake day previously collected through structured interview with a trained interviewer Several are needed (at least 3) to obtain the measure of habitual diet	As for direct observation	Low burden for participant Online versions available	Usually not appropriate for trials because of real-time researcher burden Risk of recall error Requires a trained interviewer Interviewer bias
Food frequency questionnaire	Questionnaire that assesses frequency of consumption of individual foods over a defined period (e.g., one yr) Most include 80–120 items	Energy, fiber, macronutrients, micronutrients, and additional food constituents dependent on database access (e.g., FODMAPs and gluten) Food groups	Low burden for participant Simple to administer Accounts for weekly/seasonal variation in intake Validated tools available for specific populations and specific nutrients	Usually not appropriate for clinical trials because it measures long-term dietary intake Time consuming for participant (up to 60 min) Requires mathematical skill to calculate intake using frequency categories Infrequently consumed foods may be missed because of fixed food lists Greater risk of underreporting and error compared with other methods
Validated adherence questionnaire	Questionnaire that assesses adherence to a diet (e.g., gluten-free diet).	Varies depending on the questionnaire	Low burden for participant	Usually provides an adherence score without nutrition composition data

FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

adequacy to be measured and can enable derivation of measures including diet quality and dietary diversity (42), the latter recently performed using methods for determining microbiome alpha-diversity (e.g. Faith diversity) and beta-diversity (UniFrac distance metric (43)).

Methods of dietary assessment. Dietary data can be obtained through prospective documentation (e.g., food records) or retrospective recall (e.g., food frequency questionnaire) of the type and quantity of food consumed (Table 3). Automated food and portion size identification through image-based technology can improve accuracy of data when used alongside traditional assessment methods (44), although it is not yet considered a suitable stand-alone tool (45). Mobile applications with barcode scanning facility enable rapid entry of dietary intake data, although it may not be suitable for granular analysis at the submacronutrient level (46). Dietary biomarkers, such as urinary metabolites, can be used as objective surrogate measures of recent intake (47), although application is currently limited by insufficient validation and high cost. The choice of prospective or retrospective methods of dietary data collection is determined by trial design, the dietary constituent(s) of interest, and resources available.

Collecting high-quality dietary data. One of the most acknowledged challenges of dietary research is the complexity of measuring diet. Accuracy of any dietary assessment method is limited because of the reporting error, Hawthorne effect and response bias (Figure 2), the systematic and random errors associated with coding of diet records, and the limitations associated with food composition data (48). Reporting error, at least with prospective methods, can be reduced by limiting recording duration. Most dietary trials use 3–7 days of recording, and 7 days has traditionally been deemed as sufficient in healthy individuals (49). For nutrients and foods where intakes have high within-subject coefficients of variation (i.e., eaten in widely variable amounts on different days), the number of days required to record actual intake with a high level of precision can be extreme (50). Recording duration for the greatest precision must be weighed against participant burden and the reduced accuracy resulting from "recording fatigue."

The quality of dietary data can be optimized using several approaches. Provision of clear instructions to participants for completing dietary assessments and utilization of resources to enhance portion size accuracy (e.g., food models) will improve precision. Comprehensive cross-check of data should occur as soon as practically possible after data collection. Implausible data can be identified using calculations based on low and high energy intake cutoffs (51) or predicted energy requirements (52). Collaboration with a researcher in nutrition or dietetics is recommended.

Adverse events, tolerability, acceptability, and quality of life

Although dietary therapies generally have a good safety profile compared with drugs, they may still carry some risk. Historically, dietary trials in DGBI have lacked standardized definitions of adverse events and many fail to report them at all. There has also been a focus on adverse events primarily consisting of worsened GI symptoms, with less frequent attention to extraintestinal manifestations, weight loss, or nutritional deficiencies. Adverse event data should be collected at prespecified intervals, and the reason for withdrawal should be recorded and reported.

Participation in a dietary trial can lead to unintended impacts on mental and social well-being, particularly in dietary counseling trials that mimic real-world practice. Therefore, tolerability, acceptability, and impact on food-related quality of life (FR-QoL) should also be assessed to fully evaluate the safety of a dietary intervention. Tolerability and acceptability are defined in various ways in the literature and are used interchangeably. Tolerability is commonly defined as GI tolerance but should encompass

Table 4. Online resources for dietary assessment tools

Toolkit	Country of origin	Website	Description of content
Nutritools	United Kingdom	http://www.nutritools.org	Best practice guidelines; dietary assessment tool library, including several filter options e.g. reporting method and evidence of validation; and a diet questionnaire creator
Diet, Anthropometry and Physical Activity Measurement Toolkit	United Kingdom	http://www.measurement-toolkit.org/	Description of validity, reliability, error, and bias in dietary assessment; data processing information (e.g., data cleaning and outliers); and a dietary assessment selector tool
National Cancer Institute's Dietary Assessment Primer	United States	https://dietassessmentprimer.cancer.gov/	Dietary assessment primer providing key concepts, advice on choosing a dietary assessment tool, and glossary of key terms and data processing information (e.g., day-of-week effect and energy adjustment)
Danone Dietary Assessment Toolkit	France	https://devhyp.nutriomique.org/tools/	Decision tree and matrix for method selection; recommendations for reducing error; description, requirements, and validation data for various dietary assessment tools with references; how to format data; data monitoring and quality control; data cleaning; and data analysis

Table 5. Recommendations for optimal reporting of dietary intervention trials to be used in conjunction with standard reporting checklists for clinical trials

Title and abstract	Include the name of the nutrient, food, or dietary intervention in the title and abstract
	Include the dose of the nutrient or food or the extent of achievement of the dietary intervention in the abstract
Introduction	
Background and objectives	Provide a mechanistic rationale for how the nutrient, food, or dietary intervention might affect the outcome of interest
	Provide a summary of available evidence from animal or human studies for the effect of the nutrient, food, or dietary intervention on the outcome of interest
Methods	
Trial design	Describe the intervention (nutrient or nutraceutical supplementation, food intervention, diet intervention, and individualized diet intervention; Table 1), the nature of the intervention (e.g., supplementation and exclusion), and the study design (e.g., mode of delivery, parallel or crossover) (Figure 1). For crossover trials, the washout period should be defined and justified.
Participants	Describe any nutritional (e.g., anthropometry and iron deficiency), dietary (e.g., dietary restrictions, whether naïve to specific dietary interventions), or physiological (e.g., lactose malabsorption) characteristics that were part of the eligibility criteria for participants, including how these were measured during screening and details of cutoffs for inclusion/exclusion
	Describe any characteristics of the study settings or participants that might affect the nutritional status or dietary intake of the participants, where applicable (e.g., season of recruitment, significant global events (e.g., COVID-19 pandemic), food availability, and recruitment practice over the Christmas period). Describe any relevant criteria relating to the absence or presence of food reactions and current special diet (e.g., vegetarian, vegan, and exclusion diets)
Interventions	Completely define prespecified primary and secondary outcome measures, including how and when they were assessed. Use validated tools where possible to assess clinical (e.g., irritable bowel syndrome-severity scoring system, IBS-SSS (59)) and targeted physiological end points
	Clearly define nutrients, foods, or dietary intervention under investigation (e.g., composition, dose, frequency, timing, and duration)
	Describe whether a run-in period was incorporated to allow for adaptation (e.g., starting at a reduced dose or frequency)
	For a dietary intervention study, describe the mode of delivery, that is, whether it is a feeding study or dietary counseling study (or hybrid), including whether all, most, or part of the intervention is provided to patients, and whether any individualization or personalization was implemented for individual participants
	For a feeding study where all or most of the food or meals are provided, give details of their nutritional profile, including • How energy balance and nutritional adequacy are ensured. • Details of the design of the diets, including how intake of certain nutrients, was standardized. • Meal preparation details (i.e., research dietitian, chef, or external food-catering company). • Delivery system (i.e., refrigerated or frozen meals and external delivery company or researcher delivery). • The setting in which food or meals were prepared or consumed. • Whether the consumption of additional (nonsupplied) food and beverages (e.g., alcohol) is allowed and whether there are restrictions to this. • Any other recommendations including dose distribution, frequency, timing, consumption to appetite and whether food to be consumed with or between meals. • For a feeding study, example meal plans can be provided in supplementary material.
	For a dietary counselling study, provide the following details: • How the dietary counselling is provided, including the nature (face-to-face or online and 1:1 or group) and its frequency, duration, content, and supportive material (e.g., written diet sheets, mobile apps, additional resources, including recipes and menu planning), and the similarities and differences in how this is performed for the intervention and control groups. • The person(s) responsible for the dietary counselling, their qualifications in dietary counselling, and their roles in outcome measurement
Placebo or comparator	Clearly define the comparator or placebo under investigation (e.g., composition, dose, frequency, timing, and duration)
	The extent to which the placebo or comparator are matched for nutritional composition and content of the active ingredient to the intervention
	If there is no placebo or comparator, describe measures to control for placebo responses.
Outcomes	Report dietary intake at baseline and during the intervention/control as follows:

Table 5. (*continued*)

	• Describe the dietary assessment method(s), resources used to facilitate portion size estimation where required, the number of days and items recorded, and the validity and reliability of the tool used • Whether nutrient supplement (e.g., multivitamins) intake was recorded and included in analysis. • Describe and justify the nutrition composition data used to analyze background diet, intervention, and placebo and whether any chemical analysis was performed
	Describe how adverse event data were recorded
Adherence	Describe all approaches used to maximize adherence to the nutrient, food, or dietary intervention
	Describe the method(s) used to measure adherence
	Define *a priori* the acceptable levels of adherence with supporting references where possible, and whether acceptable adherence is a factor used to define the per protocol population
Sample size	In the sample size calculation, provide details of the origin of the data used, including the effectiveness of the intervention and placebo, the variation (SD) of this where required, the anticipated effect size, and whether these are from the same or different studies.
Blinding	Attempt and report on approaches to blinding (including description of the intervention in participant-facing information), preferably double-blinding and if not, single-blinding where possible
	Describe how blinding was achieved (who was blinded and how) and report the success rate
	The extent to which the placebo or comparator are matched for presentation, packaging, appearance, smell, and taste
Results	
Participant flow	Details whether any attrition was related to challenges of consuming the intervention or control food or diet
Baseline data	Describe the baseline characteristics of the intervention and control groups including all information that is relevant to nutrition, including history of food reactions, current special diets (e.g., vegetarian, vegan, and exclusion diets), body weight, and body mass index
	Report comprehensive data on dietary intake as relevant to the intervention (e.g. nutrients, FODMAPs and fiber) at both baseline and during the intervention/control
Adherence	Report data on adherence including average adherence in both groups and the numbers achieving adequate adherence and compare these data between intervention and control groups.
Harms	Report adverse events by the allocated group, commenting any that likely relates to the nutrient, food, or diet
Discussion	
Interpretation	Discuss the extent to which the results could be explained by other extraneous features, including the effect of the intervention on intake of other important dietary components (i.e., multicollinearity) and participant expectations for effectiveness that might affect outcome
Limitations	Describe the main limitations of the dietary assessment methods and food composition databases used and implications for the interpretation of the findings.
Generalizability	Discuss applicability of research findings to dietary recommendations in the clinical setting, including primary, secondary, or tertiary care, and whether the intervention and support provided is feasible in practice
Other information	
Registration	The trial should be prospectively registered on a publicly accessible database, and the registration information provided in the article.
	If blinding of the intervention or placebo is required, this can be achieved through top level descriptions of the intervention.
Funding	Describe sources of funding and other support including supply of nutrients or foods
	Report any conflicts of interest (real or perceived) and the role of any commercial funders in study design, data acquisition, analysis, or interpretation.

FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

palatability, impact on hunger or satiety, and perception of food volume. Currently, there are no validated questionnaires for diet tolerability in DGBI. On the other hand, acceptability refers to satisfaction with integrating dietary changes into individuals' lifestyle encompassing domains such as accessibility, cost, convenience of meal preparation, and socializing. Studies have thus far used self-developed or self-adapted questionnaires that lack validation in GI disorders (41,53). A recently developed questionnaire has been partially validated to measure such domains of diet acceptability (54); however, this has yet to be used in DGBI.

FR-QoL is the extent to which the psychosocial roles of food, eating, and drinking bring enjoyment to peoples' lives (55). FR-QoL is worse in individuals with IBS who have more dietary restrictions (56); however, clinically effective therapeutic diets for

DGBI may improve FR-QoL, but this has only been formally evaluated in the setting of a personalized low FODMAP diet for IBS (53). Instruments such as the FR-QoL-29 questionnaire (57) or Satisfaction with Food-related Life Scale (58), although only validated in other populations, are easy to administer and may be incorporated in dietary trials in DGBI. Altogether, data on adverse effects, tolerability, acceptability, and FR-QoL can help formulate recommendations for real-world practice regarding the safety and long-term suitability of the dietary intervention being evaluated.

The research team

High-quality dietary research can only occur through interdisciplinary collaboration between clinicians, scientists, and bioinformaticians. Nuances of dietary research are best understood by skilled research dietitians or research nutritionists, who are increasingly undertaking senior roles in gastroenterology research. Dietitians or nutritionists should be funded, at least, to advise on trial design, deliver interventions (e.g., provide dietary counseling, design menus, and develop written resources), oversee nutritional safety, and collect and validate dietary intake data. For whole-diet trials in particular, the quality of the dietary counseling is highly dependent on the expertise of the dietitian. Statisticians familiar with statistical issues in dietary trials should also be consulted particularly for complex trial designs, sample size determination, and sensitivity analyses.

Online resources

Digital tools, which can aid in the design and execution of dietary trials in individuals with DGBI, are increasingly available. A detailed accounting of these resources is beyond the scope of this review but can be found elsewhere (59). One high-value website for clinical investigators interested in dietary trials is Nutritools.org, which provides a comprehensive listing of validated dietary assessment tools, validation details, guidance on creating new tools, and links to food databases and data resources (e.g., guidance on data sharing). Other useful websites are given in Table 4.

Recommendations for reporting dietary trials

Recommendations have been prepared for reporting clinical trials of dietary interventions (Table 5). These recommendations were developed based on the experience of the authors and consulting the CONSORT 2010 guidelines for reporting randomized trials (60), the extended statement for nonpharmacologic treatments (39), the STROBE-nut extension for reporting nutritional epidemiology (61), the International Life Sciences Institute Europe Expert Group Guidelines for reporting studies to evaluate the health benefits of foods (62), and previous Rome Foundation Working Group Guidelines for the conduct of dietary trials in functional GI disorders (1). The intention is for these to be used in conjunction with the most appropriate reporting guideline (e.g., CONSORT). Those issues that cannot be overcome should be transparently reported. To do so will not only enhance the credibility of dietary research but also offer the greatest possibility of identifying evidence-based dietary treatment options.

CONCLUSION AND FUTURE RESEARCH

Randomized placebo-controlled trials of dietary interventions are possible with sufficient attention to design and methodology nuances germane to dietary trials. Collaboration with experts in nutrition and dietetics is essential in the planning phase and for intervention delivery and the collection of high-quality dietary intake data and overseeing nutritional safety. Placebo controls and blinding are possible for nutrient supplementation, food supplementation and whole-diet interventions, and dietary confounding can be limited particularly in feeding trials. Biases are unavoidable in dietary trials but can be minimized and mitigated with appropriate strategies across recruitment and delivery of the intervention. Even with planning and support, some challenges cannot be overcome. Sample sizes required are often prohibitively high, and therefore, trials are regularly underpowered. Therefore, whether the same stringent criteria for assessing robustness of pharmacotherapy trials should apply to dietary trials for the purposes of evidence synthesis remains an issue for discussion. Researchers undertaking future dietary trials must be transparent in the reporting of design and methodology challenges and approaches used to overcoming them. Reporting of adverse events should be considered mandatory, and it is recommended that patient-centered outcomes such as tolerability, acceptability, and FR-QoL be measured for the safety evaluation of dietary interventions and therefore for informing their long-term suitability.

CONFLICTS OF INTEREST

Guarantor of the article: Kevin Whelan, PhD.
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