Design of Clinical Trials Evaluating Dietary Interventions in Patients With Functional Gastrointestinal Disorders

Chu K. Yao, BND (Hons)[1], Peter R. Gibson, MD, FRACP[1] and Susan J. Shepherd, PhD, MND, BAppSci[2]

Clear guiding principles for the design and conduct of dietary intervention trials in functional gastrointestinal disorders (FGID) are lacking. This narrative review examines the specific challenges associated with the design and reporting in dietary intervention trials. Dietary intervention trials need to address the collinearity between food, nutrients, and bioactive components that obscure the relationship between food and their effects in the gut. Randomized, double-blinded, placebo-controlled studies remain the gold standard for dietary trials, but are limited by difficulties in adequate masking of study food or inappropriate choice of placebo food/diets. Provision of study diets as the preferred delivery method can somewhat address these limitations, although allowing good adherence compared with education-based dietary interventions. Issues associated with participant expectancies and dietary behaviors can alter the true effectiveness of a diet. In addition, failure to adjust for or report baseline intake of nutrients of interest can reduce their magnitude of benefit. Bias in subjective reports and choice of measurement tools can preclude accurate assessment of food-intake data. In the design of elimination and rechallenge studies, sufficient time period and adequate exclusion of dietary triggers are essential to ensure symptoms are well-controlled before rechallenging. The route and frequency of challenging, design of test food, and/or placebo should match the aims of the rechallenge phase. Long-term efficacy data of such therapeutic diets has been poorly documented in most studies. Standardized guidelines that address many of the challenges outlined above are suggested to strengthen the quality of evidence for dietary therapies in FGID.

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INTRODUCTION

The process of designing a pharmacological intervention trial is clearly established. There have been numerous publications and guidelines by the Food and Drug Administration and other national regulatory bodies made available to improve standards of design and reporting of these pharmacological trials. For example, the STROBE Statement provides a structural guide for observational studies, the CONSORT Statement for randomized controlled trials, and the TREND Statement for nonrandomized comparative trials (1–3). Although these guiding principles are also applicable to nonpharmacological trials, there are several concepts that can be difficult to implement in dietary studies. Furthermore, no comprehensive reporting guidelines are available for dietary interventions, in general, or specifically for studies in functional gastrointestinal disorders (FGID). Hence, this narrative review aims to discuss methodological challenges and quality of reporting specific to dietary intervention trials and, subsequently, recommend standardized guidelines to enhance the quality and acceptability of future trials and their outcomes.

METHODS

A literature search was performed through Medline, CINAHL, and PubMed, using the keywords "diet," "dietary intervention/therapy/management," "feeding studies," "food challenge," as well as "placebo," "blinded," "compliance" and "adherence." The search included observational studies, randomized or nonrandomized clinical trial designs in both FGID and other clinical areas. Studies were assessed for their design and administration of dietary intervention, use of placebo, strategies for blinding, measurement of compliance, nutritional end-points, if any, and potential risks for reporting bias. Review papers on pharmacological therapeutic trial conducted in FGID were also examined and compared with dietary trials for similarities and differences.

COMPARISON OF THE DESIGN OF DIETARY AND DRUG TRIALS

There are many aspects of clinical trials that are shared by pharmaceutical and dietary studies. For example, the success of both interventions are dependent on many factors, including interactions

[1]Alfred Hospital, Monash University, Melbourne, Victoria, Australia; [2]Department of Dietetics and Human Nutrition, La Trobe University, Bundoora, Victoria, Australia. **Correspondence:** Susan J. Shepherd, PhD, MND, BAppSci, Department of Dietetics and Human Nutrition, La Trobe University, Bundoora, Victoria 3086, Australia. E-mail s.shepherd@latrobe.edu.au or sue@shepherdworks.com.au
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Table 1. Comparison of methodological considerations between drug and dietary trials

	Drugs	Food
Chemical effect on targets	Specific	Multicollinearity
Composition	Isolated substances with similar chemical and physical characteristics	Heterogeneous mixture of nutrients and bioactive components
Administration	Small dose taken whole at defined times	Consumed throughout the day
Baseline exposure	Can be absent before intervention	Continuous exposure and varying between persons
Access	No/limited access to study drugs	Readily accessible
Placebo	Easy to make	Difficult to design
Influence of pre-conceived ideas	Small-to-moderate effect	Powerful effect
Blinding	Double-blinding easy with placebo pills	Difficult and often not feasible to double-blind

between the food/drug tested and the patient, the physician and the physical setting, appropriate selection of the patient cohort, and the choice of delivery method or form of intervention (4). However, dietary trials tend to be more reactive to external variables and design difficulties in comparison with drug trials. **Table 1** summarizes the key differences in methodological concepts between drug and dietary trials.

One of the core complexities of dietary studies is that food comprises a diverse mix of nutrients and bioactive components. As a combination of whole food and diets are normally consumed, intakes are highly correlated (5). Food consumption is further complicated by dietary behaviors and determinants of these behaviors.

Furthermore, a dietary component can have functional roles in several physiological pathways. If dietary effects exerted on another pathway are not captured, an inaccurate picture of its true effects can be shown (6). In addition, comprehensive knowledge regarding the composition of food is necessary (7) to achieve a better understanding of food and its physiological effects. Yet, there are still gaps in our knowledge of food composition, such as the resistant starch content in food (8).

DESIGN OF DIETARY TRIALS AND METHODOLOGICAL ISSUES

Observational studies

The majority of data regarding the associations between nutrient intake or dietary patterns and the genesis of gastrointestinal symptoms in patients with FGID are derived from observational studies. However, the interpretation of evidence for a relationship between individual dietary components is difficult, because of several factors. First, studies that focus on the role of individual nutrients in the form of pure supplements may not capture their true effects on health as when they are consumed within a diet (7). For example, in studies of cardiovascular risk factors, high intake of saturated fat is associated with increased low-density lipoprotein levels, but this effect was not seen with the consumption of high-fat dairy products (9). When attempting to identify food culprits that contribute to adverse symptoms in patients with FGID, it is important to note that other dietary components that could be candidates for symptom induction may coexist in food. Hence, the attribution of an effect in an observational study may be hazardous. An example is the dilemma regarding symptom improvement on a gluten-free diet, as gluten and fructans coexist in wheat and rye (10,11). In addition, information obtained in, e.g., case–control surveys of dietary patterns, may not adequately capture fluctuations in dietary intake over the longer term (12). These factors alone and in combination can weaken findings of studies that rely upon identifying differences in dietary patterns of healthy compared with FGID populations, to understand the role of food components in the pathogenesis of FGID.

Dietary intervention trials

In clinical trials, issues with designing the diet of interest, participant expectancies and characteristics, controlling for and minimizing noncompliance to dietary changes, and measuring adherence can limit the validity of a research trial. Although randomized, double-blinded, placebo-controlled studies are the gold standard for accurate evaluation of successful interventions in FGID (13), they are not always achievable in dietary therapies. These design challenges and recommendations for managing these challenges are described below.

Challenges with participant expectancies and eating behaviors. Participants enrolled in a dietary trial can alter trial outcomes significantly via the strong influence of preconceived ideas. For example, food taboos or, conversely, the perception of comfort or curative properties of a food can stimulate a physiological response despite the absence of a biological basis (4,14,15). In addition, if subjects have a preconception of perceived intolerance, it may lead to an incorrect assumption of an inability to tolerate component(s) of a diet. Examples of these are patients with irritable bowel syndrome and lactose intolerance, who often believe they are intolerant of all dairy food (16).

Other behavioral determinants of food intake include the setting and style of food. For example, usual eating behaviors may be altered if one is observed while eating or if eating in a hospital setting (17). The size of meals or portions can also affect intake (18). Study participants can be influenced by mass media, friends, and health professionals regarding food choices. For example, food high in omega-3 fatty acids may be favored if individuals value their anti-inflammatory properties, and this may subsequently affect study outcomes.

Recommendations

- Where possible, ensure the setting for collecting data regarding food intake is similar to the patient's normal environment
- Record any food aversions and other food beliefs the participant may have, including reasons, to identify any response bias

Challenges with the control of background food intake. When performing dietary intervention trials, particularly where food supplements or food challenges are being evaluated, it is essential to obtain data on the baseline intake of the food or food component being challenged. A number of studies have not eliminated or quantified the nutrient or dietary component of interest in the background diet before and/or during the intervention. The consequence of this omission may lead to uncertainties regarding amount of food or nutrient (in the absence of any nutritional deficiencies) required to derive health benefits (19). Likewise, the background intake of the food component may influence endpoints in the placebo group, especially if the supplement is being used in amounts that can be obtained from food rather than in pharmacological quantities. An example of this is the evaluation of the bifidogenic effects of supplementation with fructo-oligosaccharides. As prebiotic effects are observed at amounts readily obtained in the diet, a specific effect of the supplement may well be lost if the background fructan intake is not considered. This may have been responsible for the absence of effect in a study in Crohn's disease (20). In addition, it is important to document the participant's usual dietary intake and past history of dietary therapies when controlling for baseline intake. For example, many patients with irritable bowel syndrome may have already self-excluded suspected trigger food from their baseline diet, and this may contribute to a reduced magnitude or lack of benefit for an elimination diet (21). Therefore, the incorporation of a defined run-in period before randomizing participants to a dietary intervention will not only adjust for prior dietary habits but will also allow for physical adaptations to changes in diet.

Recommendations

- Usual dietary intake, past history of dietary therapies, whether self-implemented or advised by a health professional, and the use of supplements need to be documented and considered, to control for baseline intake
- Intake of the nutrient or food component of interest, particularly in the placebo group should be quantified before and during implementation of the dietary intervention

Challenges with the design and delivery of the placebo diet. In dietary studies, the following forms of placebo are commonly employed.

- *Placebo pill:* This may be relatively easy to prepare and can be identical in appearance to the active compound. However, as food components may have familiar smell, color, or taste, the blinding can be compromised by opening of the capsules by the participant.
- *Placebo food:* There are difficulties with using whole food in their natural form because of the potential for inherent chemical diversity within the food; e.g., even two of the same variety of apple will vary in their chemical composition owing to several factors, such as variations in ripeness. Some studies have unsuitably matched test food with a different placebo; e.g., a whole kiwifruit has been compared with a glucose pill (22). In rechallenge studies, the confounding influence of other properties within the placebo food may be an issue in triggering gut symptoms. To overcome this, both test and placebo food can be manufactured to be identical for taste, texture, and appearance, but to differ only in one component. For example, the use of muffins in evaluating the specific effects of gluten was achieved by using carbohydrate-depleted gluten that had lost functionality—the muffins were of similar texture and taste, and the potential confounding effects of FODMAPs on triggering gut symptoms were avoided (10).
- *Placebo diet:* The design of an appropriate "sham" diet is complicated by the need to counterbalance the removal of a dietary component with another constituent to ensure that a similar nutritional profile is kept for both test and placebo diets (7). It is important to ensure that the number and groups of food changed between the two diets should be as closely matched as possible (23), particularly in evaluating the efficacy of elimination diets. It is also often impossible to blind the placebo diet, particularly if a dietary intervention is widely known (e.g., a gluten-free or high-fiber diet). In these cases, provision of all food is required to minimize the effect of knowledge and preconceptions. Another less satisfactory though practical solution is to use the representative of a typical diet of the study population to mimic normal eating situations (24–26).

Recommendations

- Choose a placebo that is nonbioactive and preferably has been well tolerated in other studies
- If utilizing a placebo in the form of a food item, it is desirable (a) to attain taste, texture, aroma, and appearance as close to identical to the test food item, and (b) to ensure these differ in only one component, i.e., the substance being tested
- If utilizing a placebo in the form of an entire diet, it is preferable to supply all the food. It is essential to ensure that the number and groups of food changed between the two diets should be as closely matched as possible, to achieve similar nutritional profiles

Challenges with blinding in dietary intervention trials. As alluded to above, successful blinding of interventions are rarely achieved in dietary studies, except in those testing efficacy of single dietary components. For example, with strict elimination diets, it is difficult to blind patients to what they are eliminating, and it is also difficult to provide control substitutes for the food they

eliminate. Furthermore, many studies do not actually report the success of dietary blinding, which makes it difficult to assess the strength of the findings (27).

Inadequate blinding can still occur when maximum efforts are taken to conceal study nutrients in packages or by its appearance. For example, two types of fiber (insoluble bran and soluble psyllium) and the placebo (rice flour) were supplied in identical containers to be mixed into yoghurts in a fiber intervention study in patients with irritable bowel syndrome (28). Not surprisingly, 75% of the participants were able to correctly guess the treatment they received.

Several factors can reduce the success of blinding. These might include participants accessing information from the internet, media, or other health professionals, or having prior nutritional knowledge. The behavior of an unblinded investigator must also be considered, as subjects can be influenced by behavioral cues, such as the body language of the practitioner, and form beliefs about whether the diet is credible.

Recommendations

- The success of dietary blinding should be reported
- An unblinded practitioner teaching the diets should not evaluate the end points
- Specialized teaching skills for the study investigator are required to minimize the influence of behavioral cues from the investigator on subject's perception of the sham diet

Challenges with adherence to the chosen experimental diet and protocol. Although the choice of delivery of an experimental diet is dependent on the cost and resources available, adherence to the dietary intervention is the biggest determinant of its effectiveness. A controlled feeding trial can be considered the gold standard for producing high-quality evidence, as it not only maximizes participant adherence to the intervention but also minimizes other confounding dietary habits (27,29). In such trials, all or most of the background diet is provided and controlled for the entire duration of the study. This is particularly suitable for assessing difficult-to-implement diets, such as "a very low-carbohydrate diet" (26,30) or strict elimination diets (31,32). When designing controlled feeding trials of more than 2 weeks' duration, it may be important to provide food that meets the estimated energy needs in all participants, as weight changes can impact on other physiological markers (33). Previous studies have addressed this by allocating subjects to standard diets varying in energy content (e.g., 8, 10, or 12 MJ/day) according to their requirements (34,35). In addition, discretionary food intake may occur, although most studies do not permit consumption of food not provided by the intervention (25,26). Reducing the likelihood of participants consuming discretionary food items may be reduced by providing a list of approved food (with specified amounts/quantities as appropriate) for use when eating out (35).

The only potential limitation to such a study design where all food is provided is that it may differ substantially from a participant's usual dietary habits, with consequent increase in the participant's anxiety levels and negative responses to the intervention, or vice versa (14). This may be of relevance to the FGID population where increased stress and anxiety levels can have a major impact on symptom outcomes (36). This approach may be less suitable in participants who have serious self-perceived food-sensitivity reactions. The need to monitor psychological well being in such dietary studies may also be warranted.

As an alternative to providing all food throughout the study, the use of education-based dietary interventions, usually administered by a dietician (37), or a partly controlled diet (i.e., the supply of some food(s) containing the test nutrient) (38) can be applied. This yields a lower quality of evidence, but is easier to implement. For instance, in a fiber intervention trial, participants might be counseled on strategies of how to achieve a high-fiber intake, or fiber might be hidden in the food and consumed as part of normal diet (28,39). Participants are more likely to achieve the target intake of fiber in the latter study protocol, but both these types of interventions are limited by the ability of the participant to follow dietary guidelines. They are also limited by large interindividual variations in the participant's usual intake of the study nutrient and, therefore, have less control over the exposure to other nutritional variables (40).

Recommendations

- Closely monitor participants by reviewing food diaries at regular intervals during the intervention, to assess adherence and, if required, arrange for additional consultation with the dietician or research assistant
- Where a study involves the participant being provided instructions on how to follow the experimental diet, supportive aids may be provided to optimize adherence. These may include emphasis on suitable food alternatives rather than purely removing food from the diet, and the use of pictorials or written information to reinforce understanding
- In both feeding- or instruction-based trials, report details of control and experimental diets, including similarities and differences in menu plans and nutritional analyses, for subsequent studies to reproduce their protocol or at least allow for reasonable comparison of results

Challenges of assessment of dietary adherence. Tools used to measure dietary adherence, such as subjective reporting and nutritional analysis, can be prone to error. Subjective reports of food intake are strongly influenced by response bias; subjects may provide responses that are considered desirable for the intervention goals or to obtain perceived approval. For example, participants may give perceived "healthy" responses, such as overreporting fiber intake or underestimating fat intake (41). Women and individuals with a higher body mass index are also more likely to underreport nutritional intake, particularly energy, which underestimates the intake of dietary component assessed (42). The burden of recording food intake may cause actual changes in eating behaviors or normal food consumption (43). When analyzing nutritional data, any differences in computerized nutritional composition programs need to be considered, as food composition tables may vary according to geographical locations (44);

e.g., fructose content in food differ between the nutrient databases of Food Standards Australia New Zealand (45) and United States Department of Agriculture (46).

An important first step to measure adherence is to define an accepted definition or a classification schedule of adherence, either one that has been validated or is appropriately justified. For example, most studies consider adherence as the consumption of 90–95% or more of the provided diet (47,48), but this may be lower in instruction-based interventions. The choice of measurement tools may also be influenced by whether the data collection is retrospective or prospective, and by the frequency of measuring adherence, such as daily records or a single snapshot of food intake.

Consideration must be taken when designing dietary interventions as to the type of measurement tool(s) that will be used. Examples of subjective tools are adherence questionnaires (49), food records, 24-h dietary recall, and dietary histories (50). Adherence diaries with check boxes of food consumed after assessment of returned portions have often been used in controlled feeding trials (19,26). **Table 2** summarizes the strengths and limitations of these subjective tools. Conversely, nutritional biomarkers (such as biochemical or serological changes) are not prone to bias from subjective reporting and are useful to correlate reported intake with temporal changes in nutritional status. However, these markers can be influenced by physiological factors, such as variations in absorption and metabolic pathways. In some instances, such as the measurement of the tissue content of fatty acids, dietary assessment questionnaires may be more appropriate (6).

When collection of dietary data relies heavily on the participant's ability to report and recall accurately, clear instructions should be provided with the reporting of food consumed, explaining the reasons for collecting dietary intake and motivating subjects to be honest (51). Food models or photographs may be incorporated into questionnaires to reduce recall errors in portion sizes (51). For example, the use of computer-administered questionnaires may be able to incorporate this strategy, particularly for retrospective assessment tools (52). Another strategy is to validate self-reported data with measurement of nutritional biomarkers, where appropriate, as discussed above (33). Large variations in dietary intake data can be reduced by excluding participants with implausible nutrient or energy intake during the baseline period (53). Most importantly, the choice of dietary tool needs to be well-matched with the aims and design of the nutritional intervention (see **Table 2**).

Recommendations

- Define an accepted definition or a classification schedule of adherence
- The assessor measuring dietary data should have appropriate skills in administering dietary assessment tools, to minimize interviewer-associated errors, to improve participant's comprehension of the questionnaire, and to assist in better recall of dietary information
- Nutritional biomarkers may be more useful than dietary assessment tools to determine adherence in some circumstances

Elimination and food challenge studies

The principles. A food challenge study comprises the determination of a specific induction of symptoms or a surrogate marker of a food reaction, such as elevation of a biomarker, by food or a by food component. This is often applied to situations where symptoms are intermittent with wellness in between attacks. An exception of this is the use of food challenge studies for the assessment of post-prandial symptomatology, where a short duration of fasting is incorporated to eliminate symptom triggers before challenging, such as the assessment of a high-fat meal on symptoms of functional dyspepsia (54). Issues associated with challenge studies are addressed in the "rechallenge" section below.

In general, the symptomatology of FGID is, by definition, chronic. This necessitates an initial "dechallenge" phase by the use of an "elimination diet" to minimize or alleviate pre-existing symptoms, followed by the food challenge, better described as "rechallenge," with the expectation that symptoms will redevelop specifically in association with food or with food components to which the subject is intolerant. The results of the food challenges will ultimately determine the long-term therapeutic diet for the management of the symptoms. Additional studies (if available or possible) would then be required to determine the pathogenesis of the specific reaction (an allergy, hypersensitivity, pharmacological reaction, or intolerance). **Table 3** summarizes some of the factors for consideration in the three stages of the elimination–rechallenge intervention.

Design of the elimination diet phase. As previously described, the purpose of an elimination diet is to minimize or abolish the patient's symptoms. If the diet does not achieve this, then the putative offending food is still present, the duration of elimination is insufficient or the symptoms have little to do with specific food. Hence, the two major issues in this phase are the design of the diet and its duration, as outlined in **Table 3**. Food triggers may be all-or-none in their effects (such as gluten) or dose-dependent (such as FODMAPs). Thus, elimination diets may fit anywhere within the spectrum of one completely devoid of food triggers (such as an elemental diet) to one that only reduces the dose of putative triggers (such as the low FODMAP diet), through to one that restricts one component only (such as a gluten-free diet). Diets employing total exclusion of potential trigger food may be anticipated to have a higher rate of symptom resolution. However, issues with diet palatability and large drop-out rates are to be anticipated. In addition, the optimal or minimal duration of following the elimination diet is important, as different triggers appear to have different "washout" periods, as described in **Table 3**.

Recommendations

- A full definition of the structure and duration of the diet is needed
- The drop-out rate during this phase should be reported

Design of the food challenge phase. In the challenge/rechallenge phase, the goals can be twofold: first, to identify the type of dietary

Table 2. Summary of measurement tools for dietary intake and considerations of their strengths and limitations

Method	Methodology	Advantages	Disadvantages
Prospective			
Direct observation	Consumption observed with known quantities of food provided. Quantity of remaining food accounted for to determine final consumption data	Enables qualitative and quantitative assessment of nutrients consumed Validates recent reported intake from other methods	Expensive May not reflect usual intake May induce behavior change
Weighed or estimated food records	Written and verbal instructions are given on how to weigh and record all food and drink consumed for a specified time period—7 days ideal, but 3 days including 1 weekend day considered representative	Requires training of participants Short term intake assessed Considered "gold standard" for dietary assessment	Time consuming Burdensome to maintain Difficult to measure food eaten away from home accurately
Food diary	Participants trained to record in a prepared diary all food and drink consumed for time period specified (usually 3–7 days). Recorded as weight/volume or household measures or food models (diagrams pre-provided describing serving sizes for comparison). Reporting must occur at time of consumption. Interviewer clarifies entries at end of assessment period	Not interviewer-dependent Not subject to recall errors Omission of food may be minimal when conducted properly	Trained staff required for data analysis Information biased to motivated volunteers May induce behavior change Requires diligent recording—may be affected by motivation, literacy Reliability may decrease over time as respondent fatigues
Retropsective			
24-h diet recall	Participants recall all food and drink consumed on previous day. Interviewer asks specific questions regarding recipe ingredients, food preparation, brand names of commercial products. Interview conducted in person or over the telephone (49)	Quantitative assessment of recent nutrient intake Short-term memory required Not subject to behavior change bias Personal contact for data clarification No literacy requirement of respondent Useful for characterizing the average intake of a group or population, or for classifying individuals into quartiles of nutrient intake	Requires specialized nutritional assessment skills for interview May not reflect usual intake Less frequently eaten food may not be identified Portion sizes may be difficult to ascertain Does not account for seasonal variations in nutrient intake Needs repeated measures over period of time to increase accuracy
Food frequency questionnaire (FFQ)	Participants asked to record (usually in a tick/check box) how frequently individual food items or food groups are consumed. Quantities consumed usually also recorded (49)	Self-administered Inexpensive and quick Useful for large cohort studies Long-term intake assessed Captures habitual intake over a longer period (from 1 month to 1 year) Can be used to target or quantify specific nutrients or aspects of food intake	Requires careful validation May not be applicable to study population Number of food items –determines comprehensiveness –too many items may cause confusion –too few options may cause high aggregation of data Quantitative analysis difficult Not open-ended Long-term memory required Tendency to overestimate nutrients due to overestimation of frequency of ingestion of a food

component and/or food that provokes gut symptoms and, second, to determine the threshold for symptom induction.

The process of rechallenging an eliminated food or food substance should be done slowly in a step-wise process and in gradual doses if the goal is to assess tolerance. A washout period should be implemented to attain symptom control with the continued elimination diet before the next challenge (55). Evidence regarding the ideal frequency of challenges and the period between each challenge remains obscure. Frequency of challenges must be considered to minimize the cumulative effect of food or food substance (32,56,57).

Double-blinded, placebo-controlled food challenges are the preferred method to identify food reactions (58). However, the method used for blinding, route of challenge, as well as the design of challenge or placebo ingredients (**Table 3**), have been poorly documented in many food challenge studies, reducing the quality of evidence. Open challenges are of poor diagnostic value if they are used on their own to confirm reactions to food, but can be useful as negative predictors to liberalize long-term dietary restrictions (55). Special attention should also be given to control for factors that can adversely interact with challenges, such as concurrent medication use, alcohol intake, and physical activity levels (58). Ultimately, the challenge protocol designed should also be practical to implement in a clinical setting.

A major issue with the measurement of subjective endpoints of adverse symptoms in patients with FGID is the nocebo effect,

Table 3. The three phases of elimination diet-rechallenge studies

Components of study phase	Design considerations	Examples	Situations used, success, and deficits in literature
Elimination diet phase			
Structure and definition of diet	Complete exclusion of large number of suspect food	Oligo-antigenic diet "Few foods diet" (dietary staples allowed—meat, rice, fruit (usually pears), spring water)	Investigation of food allergy or hypersensitivity or where a large number of food triggers are suspected (54,59,62,63) Deficits: inconsistencies in food eliminated observed even within the same type of elimination diet (59,63)
	Complete exclusion of whole food. Liquid formula of fully or partially digested energy sources	Elemental or polymeric diet Hydrolysed (usually amino acid) formula replacing intact or allergenic protein	Indicated when symptoms fail to improve with other forms of elimination, but dietary triggers are suspected
	Restriction of suspected food triggers to intake below threshold likely to cause symptoms	Low allergenic diet Low FODMAP diet	Food with high content of putative triggers (e.g., food chemicals, FODMAPs, gluten) substituted with low content alternatives
Duration for elimination	Determined by: Extent of food exclusion Severity of baseline symptoms in study population (64) Previous evidence for optimal symptom control	≥1 week	Success: low FODMAP diet—greatest symptom control attained after 1 week (65)
		≥2–6 weeks	Success: gluten-free diet—70% report symptom reduction after 2 weeks (66,67)
		4–6 weeks	Success: restricted chemical diet—77% reported ≥50% improvement (55)
Dietary endpoints	Validated measures for symptom assessment	IBS-severity scale using visual analog scales±adequate relief of global IBS symptoms (68)	Majority of elimination studies in FGID used validated measures (21,69–71)
	Where possible, incorporate objective markers for improvement	Rectal sensory threshold (barostat studies) Breath hydrogen measurements	Symptom improvement on IgG4-exclusion diet correlated with greater tolerance of rectal distension (72) Reduced breath hydrogen correlated with symptom improvement after low vs. high FODMAP diet (24)
	Objective or arbitrarily predefined criteria specified	50% Symptom reduction acceptable as clinical response (68)	≥50–80% reduction in both global and/or individual symptoms from baseline symptoms (55,69,70,73) Deficits: most dietary trials define improvement as "asymptomatic" (54,74)
Rechallenge phase			
Rechallenge aims and protocol design	Identification of suspect food	Open food challenges followed by double-blinded placebo-controlled food challenges Placebo and test food administered at random and on separate days	Success: challenges firstly done openly in food groups with similar "antigen" content, then double-blinded placebo-control of food in food groups with positive reactions to reduce burden of challenge (54) Random challenges of test/placebo on separate days minimized placebo reactions (5% patients had positive reactions to placebo in the study using this protocol) (55)
		Single food challenges in specified order	Deficits: specific details of amount of food challenged often not reported (59,75)
	Assessment of threshold for symptom provocation or tolerance	Stepwise and gradual reintroduction of single food/food component at varying quantities	2-week FODMAP challenge—starting dose of 1/3 "average" dietary intake for 3 days→increased to 2/3 for 3 days→final total dose of estimated "average" dietary intake for remaining period (32)
	Route of challenges	Oral	Preferred method for evaluation as food is normally ingested arriving in stomach
		Nasogastric/tube feeding	Prevents unblinding due to taste, texture, aroma (57) Allows examination of local physiological responses (76)
		Direct methods of administration into mucosal (e.g., colonic provocation test)	Allows objective identification of gastrointestinal food allergy reactions (77)

Table 3 continued on following page

Table 3. Continued

Components of study phase	Design considerations	Examples	Situations used, success, and deficits in literature
Food challenge amount and frequency	Upper limit or lower limit of normal dietary intake	16g daily intake of gluten challenge for 6 weeks (37)	Symptoms induced in 68% patients with IBS (37)
	Same dose for each challenge regardless of food type	"Allergens" or hypersensitive reactions	The positive diagnostic yield was 6% in one study using this challenge method (74) Deficits: this method does not take into account that different foods are consumed in different quantities
	Washout period for symptoms to normalize before next challenge	Short washout period, e.g., ≥3 "symptom-free" days	Food chemical challenges (55)
		Longer washout periods, e.g., 1–3 weeks	Challenges with food components implicated in immunologic or unclear pathways of symptom induction (37,69)
Control of blinding and placebo response	Form and physical structure of food challenge	Freeze-dried food in capsules	Deficits: does not detect oropharyngeal reactions (78) Encapsulation reduces absorption rate and can delay symptoms
		Food extracts hidden in food vehicles	Good choice of food vehicles, e.g., soups (79),, elemental formula drinks (78), or gluten or whey in muffins (37)
	Design of placebo—inert and well-tolerated	Potato starch Sucrose Glucose Xylose	Positive reactions to potato starch occurred in 13% subjects (55) Positive reactions to sucrose occurred in 17% participants (55) 15–63% subjects reacted to glucose in three studies (54,74) No reactions from xylose reported in two studies (69,70)
Endpoint assessment	Validated symptom measurements or objective endpoint if possible	See above	See above
	Duration for symptom assessment after antigen exposure	Observation period for symptoms ranged from few hours to few days (80)	Gastrointestinal symptoms persisted for median 3 (range 1–8) days after milk and wheat challenges (11,69,70)
Modified long-term diet			
Long-term protocol	Complete exclusion of food with positive reactions. Challenges can be repeated to eliminate nocebo or confirm positive challenge	Food with positive challenges avoided and retested 2–3 months later (75)	Success rate in three studies: 98–100% participants reported symptom improvement (69,71,75) Few ($n = 2$) studies repeated challenges to confirm positive reactions (59,75)
	Follow-up duration	Range of follow-up duration between 4–24 months (69,70,75,80)	Adherence to diet decreases with duration of elimination, but not many report adherence rate (71,75)

Design factors for considerations with evidence of success and limitations.

a phenomenon defined as the worsening of symptoms as a result of negative expectations of being challenged and not from the content of the placebo food (**Table 3**). This can perhaps explain some of the inconsistencies in the literature. Lessons from studies in food allergy have demonstrated the importance of objective endpoints, such as the measurement of a wheal-size in a skin-prick test.

An important consideration is the duration after exposure to the challenged food for the measurement of endpoints (**Table 3**). This will vary depending on what the challenge substance is, dose, patient phenotype, and type of symptom response expected. Conducting a pilot study before embarking upon a definitive study may be helpful to determine the expected symptom generation window and, therefore, the optimal duration for endpoint assessment. In comparative studies, assessments in healthy controls must be taken at the same time points as in the FGID population.

Recommendations

- A double-blinded, placebo-controlled challenge protocol is ideal for identifying adverse food reactions
- The rechallenging process should be executed in a step-wise process and in gradual amounts
- An adequate washout period should be implemented to attain symptom control
- Frequency of challenges should be designed to minimize the cumulative effect of challenge dose

Table 4. Supplementary checklist for design of dietary intervention trials

Participants	1. Describe baseline characteristics of active treatment and control groups, specifically any history of food reactions or perceived intolerances and body weight.
Experimental protocol	1. Dietary trial should be registered. 2. Clearly provide rationale for dietary intervention. 3. Describe how pre-intervention dietary intake (of food, nutrient, or other dietary component) was measured. Is a run-in period incorporated to allow for dietary adaptation? 4. Describe steps taken to randomize and ensure blinding of participants and/or investigators, where possible. 5.Define participant adherence to intervention. a. Describe strategies used to improve adherence. b. Describe the dietary assessment tool(s) used, with justification. State the nutritional program used to analyze data. c. Report on participant compliance rate. d. Are measures taken to exclude data or subjects who are non-adherent? 6. Provide details on controlling confounding factors, such as medication interactions, physical activity. 7. Describe sources of funding and other support (such as supply of food).
Experimental diets	1. Define whether all, most or part of the diet is provided to patients. 2. If all or most food provided, give details of types of food (meal plans) and nutritional profile. a. Give details on how energy balance and nutritional adequacy are ensured. b. Describe the setting in which food was prepared or consumed. c. Is consumption of food not supplied allowed? Provide steps taken to control for discretionary food intake. 3. If no food is provided in the interventional study, explain how diet will be controlled for. a. Give details on similarities and differences of dietary education between intervention and control groups. b. Document qualifications of clinical investigators and their roles in relation to intervention. Is there a dietician in the team? c. Who administered the intervention? 4. If intervention involves nutrients or whole food, is the test food physically matched with placebo and how are these consumed? 5. If intervention involves a whole diet, is there a control/sham diet? a. If not, describe measures to control for placebo responses. b. Apart from dietary component tested, are the test and control diets similar in nutritional content?
Discussion of findings	1. Consider issues of multicollinearity with other nutrients, participant expectancies and discuss limitations of tools used. 2. Discuss applicability of research findings to formulating "real-world" dietary recommendations.

- Factors that can adversely interact with challenges such as concurrent medication use, alcohol intake, and physical activity patterns should be considered
- Measure endpoints in an appropriate time frame after exposure
- The adequacy of blinding, design of the food ingredient and its route for challenging, as well as how other confounding influences were controlled should be described

Follow-up phase. Once response to food triggers and/or the tolerance threshold has been established, the next step is to determine the long-term therapeutic diet ("modified elimination diet") for the management of gastrointestinal symptoms (**Table 3**). There is a paucity of long-term data, as several studies do not report on follow-up data or cease further investigations in patients whom dietary triggers have been identified (21,59,60). Adherence to such diets in the long run is an issue, particularly as significant changes to dietary habits can impact on lifestyle and other aspects of well being (61). The true benefit of the elimination diet approach should be judged by its long-term efficacy (**Table 3**).

Recommendations

- Longer-term outcomes should be reported
- Indications of the duration of the need for such dietary restrictions are desirable

Safety issues

Although diet has less of a potential to elicit fatal side effects with the exception of food anaphylactic reactions, safety considerations still need to be incorporated. For example, in light of restricting large amounts of food, care should be taken to ensure nutritional adequacy is maintained, particularly for those in the early life cycle or with specific nutritional needs (33,62). This is more likely to assist in adherence to the dietary therapy as well as to mimic conditions as in the "real world," to improve application of findings. Reporting of adverse events in dietary studies should have the rigor of that in pharmacological trials, but seldom does.

Recommendation

- Adverse events should be sought and reported

CONCLUSION

The design of dietary studies in patients with FGID has many challenges, which have seldom been met in published data. One way to improve such performance is to provide guidelines for the optimization of study design, interpretation, and reporting. Suggested guidelines are shown in **Table 4**. Inadequacies of the design and reporting of such trials largely stem from difficulties in manipulating the diet, food or their components, blinding, and adherence to modification of dietary habits. Translation of nutritional research into practice can also be hindered by the interpretation

of findings, namely interactions from other nutrients explaining observations, effects of participants being involved in clinical trials, and practicalities of implementing these observations in the real world. Given these difficulties, perhaps less stringent criteria for assessing the robustness of dietary trial methodology in comparison with pharmacological trials may be more appropriate. However, dietary trials for the FGID population should still primarily strive to incorporate a randomized, double-blinded, placebo-controlled study design as the highest quality possible of evidence. Adequate blinding or design of placebo diets may be achieved by either manufacturing nonbioactive food vehicles differing in only the test food component or placebo, or by the provision of all food within a sham diet. A defined run-in period to quantify or control for baseline intake of the nutrient studied will minimize confusions between the therapeutic dose of a food and its effects. Reporting across all studies should consistently include information on the nutritional differences of both experimental and placebo diets, the success of blinding of diets and occurrence of any adverse events. Elimination and rechallenge studies should focus on designing long-term follow-up to address the feasibility and benefit of such dietary approaches.

CONFLICT OF INTEREST

Guarantor of the article: Susan J. Shepherd, PhD, MND, BAppSci.
Specific author contributions: Chu K. Yao contributed to collation and analysis of studies for review, drafting, and editing of the manuscript, and has approved the final draft submitted. Susan J. Shepherd and Peter R. Gibson contributed to drafting the manuscript and have approved the final draft submitted.
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Potential competing interests: Chu K. Yao received research funding from Yakult. Susan J. Shepherd and Peter R. Gibson are the co-owner of the trademark, "FODMAP". The trademark is no longer enforceable because of widespread accepted usage of the term (we do not believe that this is now a conflict). Susan J. Shepherd is the co-author of a book on the management of food intolerance, a shopping guide for food intolerances, and four cookbooks for food intolerances. She is also the co-director and shareholder of FODMAP P/L, which has the trademark "FODMAP FRIENDLY," and is the co-director and shareholder of the Low FODMAP Food Company P/L (these companies have nil income). She also had dietetic private practice specializing in FGID. Peter R. Gibson is the co-author of a book on the management of food intolerance. He received consulting fees from Vital Foods and received lecture fees from Meat & Livestock Australia. He received research support from Yakult.

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