The challenges of control groups, placebos and blinding in clinical trials of dietary interventions

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Abstract

High quality placebo-controlled evidence for food, nutrient or dietary advice interventions is vital for verifying the role of diet in optimising health or for the management of disease. This could be argued to be especially important where the benefits of dietary intervention are coupled with potential risks such as compromising nutrient intake, particularly in the case of exclusion diets. The objective of this paper is to explore the challenges associated with clinical trials in dietary research, review the types of controls used and present the advantages and disadvantages of each, including issues regarding placebos and blinding. Placebo-controlled trials in nutrient interventions are relatively straightforward, as in general placebos can be easily produced. However, the challenges associated with conducting placebo-controlled food interventions and dietary advice interventions are protean, and this has led to a paucity of placebo-controlled food and dietary advice trials compared with drug trials. This review appraises the types of controls used in dietary intervention trials and provides recommendations and nine essential criteria for the design and development of sham diets for use in studies evaluating the effect of dietary advice, along with practical guidance regarding their evaluation. The rationale for these criteria predominantly relate to avoiding altering the outcome of interest in those delivered the sham intervention in these types of studies, whilst not compromising blinding.

The challenge of control groups in dietary research

Diet can impart favourable effects on health and disease risk, and can be used in the management of disease. Rigorous research design and methodology is essential in informing the precise influence of diet in each of these realms. The gold standard method for investigating the effectiveness of a therapeutic intervention (for example, drug, nutrient, food, dietary advice) is the randomised, double-blind, placebo-controlled trial (RCT). The design and conduct of drug trials is closely regulated by national and international bodies such as the Medicines and Healthcare products Regulatory Agency, the Food and Drug Administration and the European Medicines Agency. In contrast, guidelines on conducting clinical trials of dietary interventions (i.e. food or nutrient intervention, or dietary advice) do not exist.

Use of placebo controls is relatively straightforward in drug and nutrient trials as products (e.g. capsules, liquids or powders) can be developed that mimic the drug or nutrient without containing the active ingredient. However, placebo design presents a major obstacle in food or dietary advice trials, and this has contributed to a paucity of placebo-controlled trials investigating the effect of dietary interventions in healthcare. This review evaluates the types of controls used in dietary trials and presents the advantages and disadvantages of each using examples from the literature. Other relevant issues such as blinding, adherence and biases will also be discussed. An example of the development of a novel placebo (sham) diet for use in an IBS trial is provided, that has until now not been detailed and will prove beneficial for future placebo-controlled dietary advice intervention trials. A glossary of terms is provided in Table 1.

Controls, placebo and blinding in dietary research

Benchmarking the physiological and clinical effects of an intervention group against a control group is essential for providing unambiguous evidence that the intervention is superior to not having the intervention. The effects of a drug, nutrient, food or dietary advice can be explained by its pharmacological, toxicological and/or nutritional properties. In addition, the effects can also occur due to the interaction between the individual, the prescriber (or the researcher) and the drug, nutrient, food or dietary advice creating the placebo response [(2)]. In addition to these, food interventions or dietary advice can exert placebo effects that are influenced by previous exposure, expectation and response to particular foods, personal and cultural beliefs regarding food and diet, sensory satisfaction, taste preferences and the support and reassurance of the dietitian or nutritionist providing the advice. The response to a food

intervention or dietary advice is therefore the sum of its impact on nutritional physiology/biochemistry and the complex factors impacting the placebo response [3], further highlighting the importance of placebo control in trials of these interventions. Bearing this in mind, there are a number of possibilities when considering the use of controls in dietary intervention studies.

Uncontrolled trials

Uncontrolled trials of food or dietary advice evaluate the effect of an intervention without a control group, and conclusions are based on the paired changes that occur within the intervention group only. Although uncontrolled trials fall outside the recommendations by The International Conference on Harmonization guidelines [4], it has been estimated that one third of all clinical trials are uncontrolled [5]. This approach is subject to limitations based upon the lack of opportunity to compare against a group not receiving the intervention. Therefore, it is impossible to exclude that any changes occurring over the duration of the intervention would not have occurred had the intervention not taken place, although inter-subject variation is controlled for when undertaking paired comparisons.

Despite these limitations, uncontrolled trials are generally easy and cheap to conduct and are appropriate for the evaluation of novel, untested, dietary interventions. They are therefore useful for exploratory studies that inform the design of larger controlled studies. Uncontrolled trials may be appropriate in patient groups in whom there are ethical risks of not providing an intervention, such as those at nutritional risk e.g. oncology [6], paediatrics [7] or in diseases with rapid or fatal progression [5]. Uncontrolled trials may also be appropriate in extremely rare conditions where a sufficient sample size for both an intervention group and a control group is impossible. Therefore, although uncontrolled trials are a source of only very weak clinical evidence [5], they may be appropriate in some isolated cases. Finally, although the placebo effect is impossible to measure in uncontrolled trials, and may be particularly strong for subjective endpoints such as self-reported symptoms, it could be argued that uncontrolled trials suitably represent the effects of dietary intervention achievable in real life, as the placebo effect is commonly applied as part of many therapeutic interventions in nutrition and dietetic practice [8].

Controlled trials

There are four common types of controls utilised in intervention trials of nutrient, food or dietary advice. The following section will describe these approaches and address the advantages and disadvantages of each.

No-treatment, wait list, external and historical controls

The first type of control is the "no treatment" control, in which participants do not receive the intervention, nor do they receive a placebo or comparative intervention. Despite having no intervention or placebo, it is important that participants in the "no treatment" control group are evaluated using the same outcome measures at the same timepoints as those receiving the intervention to lead to a comparable Hawthorne effect between groups (the effect of measurement on response to measurement) (Table 1). Although this approach could be considered superior to the uncontrolled trial, one key issue is that participants are unblinded i.e. they have knowledge of their treatment assignment. This can result in significant expectation bias in the intervention group (i.e. the expectation of benefit could lead to more favourable outcome in those receiving treatment), which also exists in uncontrolled trials. However, there is a risk of uneven expectation bias between the "no treatment" control group (i.e. the expectation of lack of benefit could lead to less favourable outcome) and the intervention group. This may be particularly important in trials of treatments with subjective outcomes (e.g. quality of life, symptom reporting).

A special type of no treatment control that is commonly used in dietary intervention studies is a wait-list control (i.e. patients waiting for a routine appointment) who present a convenient "no treatment" control population [9-11]. The advantage of this is the ethical benefit of patients obtaining treatment who are seeking care. However, the disadvantage is that these patients are not randomised to this group, leading to a risk of allocation bias. Furthermore, at least according to behavioural research, the use of wait-list controls can overestimate treatment effect, as they change less than expected for individuals who are concerned about their behaviour [12]. However, other evidence suggests the expectation of future intervention in wait-list controls could also lead to unwanted improvement in endpoints, essentially leading to an underestimation of effect in the treatment group. For example, wait-list controls in energy restriction studies have lost weight [10], in coeliac adherence studies they have reported improvements in quality of life [11] and in irritable bowel syndrome they have reported symptom improvements [13]. Despite this, "no treatment" controlled trials, including those utilising wait-list controls, are appropriate for trials with objective outcomes that might be

less likely to respond to biases (e.g. the effect of a dietary intervention on blood cholesterol) and in trials where blinding is difficult [4].

External or historical control groups utilise participants external to the trial. For example, in studies using hospitalised patients, historical data is collected for the external group from medical records. Of course this can potentially be limited by the level of detail that can be acquired from previously documented records. Externally or historically-controlled trials are generally also hazardous as it can never be guaranteed that the controls and the treatment group are truly sampled from the same population. Interestingly, untreated historical-control groups are reported to have worse outcomes than concurrent control groups, probably reflecting a selection bias [4]. Overall, this approach is generally not recommended other than in situations where no other control group is available [4].

Active comparator groups

A third type of control is an active comparator group. In most instances where a dietary intervention is compared with another active intervention, the comparator group (for it is no longer an inactive control group) receives a standard treatment. For example, in a food intervention study investigating the effect of prunes on constipation, the treatment group were compared with an active comparator group in which another food is consumed, i.e. psyllium [14]. In dietary advice studies, an active control might receive dietary advice that is known to have some established efficacy and is used as current best practice. For example, standard low fat dietary advice has been compared with Mediterranean dietary advice in a large multicentre trial investigating the effect of diet on cardiovascular risk (PREDIMED) [15]. In Crohn's disease, the use of whole protein enteral nutrition has been used as an active comparator when evaluating the effect of elemental enteral nutrition on achieving remission [16], and standard advice to reduce fibrous foods in active Crohn's disease was used as an active comparator to a novel low microparticle diet [17]. Standard nutritional counselling has also been compared with enteral nutrition for post-surgical patients with GI cancer [18]. In irritable bowel syndrome, dietary advice considered best practice at the time has been used as an active comparator when evaluating the effect of a diet low in fermentable carbohydrates (low FODMAP diet) [19,20].

Standard treatment might also consist of standard physician care, for example when evaluating the effect of dietary intervention on weight and cardiovascular disease risk factors

[21]. Whilst representing real life clinical practice, standard physician care may be limited by differing follow up frequency between groups resulting in an uneven Hawthorne effect. For example, in the study of dietitian-led team care incorporating Dietary Approaches to Stop Hypertension (DASH) advice versus standard physician care on cardiovascular risk, the active comparator group were asked to see their physician for follow up care with no other follow up throughout the six month duration of the trial [21].

Trials with active comparators are used to establish the effect of a new dietary intervention as equivalent or superior to current practice (dietary or otherwise) and might be considered more ethically acceptable as all participants receive active treatment at the outset. This is particularly relevant in trials of patients with serious morbidity [22]. Interestingly, physicians are more likely to recommend participant involvement in, and are more likely to prescribe drugs tested in, trials with active comparators than placebo-controlled trials [23], and patients prefer involvement in active comparator trials than placebo-controlled trials when evaluating drug efficacy [24]; whether this is also true for dietary trials is unknown.

One problem with an active comparator trial is the difficulty of applying homogenous advice across all the participants in the comparator group, particularly those that utilise standard care. For example, advice to implement a high fibre diet in the active comparator group will likely vary from patient to patient according to habitual fibre intake and dietary preference. This is also commonly the case when patients in an active comparator group receive standard medical care. Another issue that has arisen is when final evaluation reveals the composition of the intervention diet is not sufficiently different from the active comparator diet; a proposed point of weakness of the PREDIMED trial [25]. Poor adherence of participants within the active comparator group can also be a challenge.

Blinding the active comparator diet can be difficult, which leads to a risk of uneven expectancy distribution and reduces internal validity of the trial. This may be particularly so where the active comparator is ‘standard advice’ that has been commonplace in clinical practice for some time (e.g. low fat dietary advice for cardiovascular disease). Previous exposure to ‘standard advice’ should be considered as an exclusion criterion in these situations to help minimise unblinding.

Placebo controls

The fourth and final example of a control is the placebo control. This is a "dummy" or inert treatment that appears as identical as possible to the intervention of interest. For example, in a food intervention study investigating the bone protective effect of dried plums, these were compared with a placebo control group which was allocated a different food with no bone protective properties, i.e. apple [26]. The placebo-controlled trial is considered the most robust of clinical trials. Randomisation and double blinding enable minimisation of subject bias and observer bias [27]. Where disease risk factors or disease endpoints are of interest, placebo controls also specifically help to account for natural progression of disease that would occur had the intervention not been prescribed [27]. This type of control is generally easily accomplished in drug trials as well as in nutrient or nutraceutical supplementation studies. For example trials evaluating prebiotics [28, 29] or specific nutrients [30,31] can incorporate a placebo control in the form of a capsule or sachet produced to replicate the intervention in appearance and taste.

Conducting placebo-controlled trials in food interventions or dietary advice interventions is, however, significantly more challenging. For example, there is a multitude of studies that investigate the effect of whole diet alterations (i.e. multiple contemporaneous alterations to the diet) on disease endpoints such as Mediterranean diet for improving cardiovascular health, the Atkins diet and Nordic diet for modulating weight, or the low FODMAP diet for managing symptoms of irritable bowel syndrome. However, placebo-controlled trials of whole diets are extremely rare largely because of the difficulties firstly of using a placebo control that does not significantly alter the outcome of interest and secondly of maintaining blinding.

There are two methods by which a successful placebo control can be applied in studies of whole diet alteration trials. Firstly, feeding studies can be undertaken that administer all food and fluid to participants in the trial. The placebo control in feeding studies can be created bespoke for the purposes of the trial. It is developed to be ‘inert’ in nature, and is nutritionally matched in all aspects except for the active component being investigated [32]. There is, therefore, a lower risk of controls experiencing improvements in the outcome of interest (e.g. plasma cholesterol or IBS symptoms) compared with active comparator trials. Furthermore, placebo controls in feeding studies can be created to be almost indistinguishable to the intervention. For example, in a placebo-controlled crossover feeding study that evaluated gluten-free, casein-free diets in autism, most parents of children could not distinguish the

placebo diet from the experimental diet [33]. In this feeding study, all meals and snacks were prepared and provided to patients for 12 weeks, and diets were individually adapted based on food preferences. With extreme effort both the patient and the investigator can be blinded to both diets. However, feeding studies are burdensome for the researcher in terms of time and economic costs and are therefore often short-term (e.g. <1 week). These factors, in addition to the artificial nature of total food provision, means that feeding studies have limited external validity as in routine clinical practice patients are not fed a therapeutic diet in a controlled environment.

Secondly, it is possible to conduct placebo controlled studies of whole diet alterations using dietary advice. Dietary advice studies have the advantage over feeding studies of being representative of what is achievable in 'real life' settings. Typical difficulties encountered in everyday practice, such as non-adherence [34,35] and the potential for information to be misconstrued on transmission from practitioner to the patient, are replicated in these types of trials. As well as generally being less burdensome in terms of cost and time these types of trials could be argued to have greater clinical validity than feeding studies.

A placebo control can be incorporated into dietary advice studies by using a re-supplementation control, where the same dietary advice is given to participants in both the intervention and control groups, followed by re-supplementation of the excluded food component to the placebo group. One study has taken advantage of this study design in order to investigate the impact of the low FODMAP diet on symptoms and immune function [36]. Following a low FODMAP diet run-in period for all patients, the placebo group received fructan supplementation in order to increase FODMAP intake back to habitual levels whilst the treatment group received placebo sachets (and thus were on a low FODMAP diet). A similar design was applied in a study investigating the effect of gluten supplementation on gastrointestinal symptoms and fatigue in participants with self-reported gluten intolerance. After a 2-week run-in period of a gluten free diet, the placebo group received gluten in order to normalise gluten intake, whereas the treatment group received placebo (and thus were on a gluten free diet) [37]. These types of re-supplementation studies present a novel way of incorporating a placebo control in the evaluation of a dietary advice intervention. Re-supplementation studies are only possible if the dietary components of interest are available in supplemental form, and it assumes the components exert the same biological effects when supplemented compared with when consumed in the diet.

Alternatively, dietary advice trials can be placebo-controlled with the application of sham dietary advice. In this case, dietary advice is provided that is formulated to modify food intake without altering intake of nutrients or the specific food component being investigated. There is a paucity of research studies utilising sham diets, probably because of the difficulties of formulating and administering such a diet.

There are at least seven sham-controlled dietary advice RCTs investigating the effect of whole diet interventions reported in the literature (Table 2) [38-45]. Most evaluate the effect of an exclusion diet in gastrointestinal conditions, are of considerable size and are up to 16 weeks in duration, a length of time which broadly reflects clinical practice. The rationale for the choice of foods included in the sham diet in these studies is based on self-reported tolerance [40], the patient's usual diet [41], is relatively arbitrary [38,39,42,43] or excludes another dietary component [44]. For example, one study in patients with Crohn's disease reduced microparticle intake (inorganic calcium, food additives titanium dioxide and silicates) and compared it with a group that were provided sham dietary advice that included avoidance of the food additives sulphates and sulphur dioxide [44].

Overall, very little information is provided on the design of the sham diet, and nutrient intake is not routinely measured to confirm its equivalence to the treatment. This is imperative in dietary studies where multiple dietary factors have potential to impact on endpoints (e.g. carbohydrate, protein and fat in cardiovascular disease) [46,47]. Although collinearity is almost inevitable in dietary studies (e.g. altering intake of carbohydrate will lead to a change in the intake of other nutrients), confirmation that there is a clear difference in intake of the dietary component of interest between the sham diet and intervention diet is vital. There is a recommendation that the number of foods removed in a sham exclusion diet be comparable to the intervention diet [3], however detailed guidance for development and implementation of sham diets is scarce.

Design and development of a sham diet for use in a placebo-controlled low FODMAP dietary advice trial

Here, the design and development of the first ever sham diet for use in a low FODMAP dietary advice RCT is reported, in order to illustrate how the challenges described can be overcome, and to provide practical recommendation for sham diet development in other

317 settings. The low FODMAP diet is an exclusion diet which has demonstrated effectiveness in
318 reducing symptoms such as abdominal pain and bloating in irritable bowel syndrome [48, 49]. It
319 requires restriction of a number of short-chain carbohydrates that are ubiquitous throughout
320 the human diet, and a majority of evidence of its effectiveness is based on dietitian-led
321 dietary advice provided to participants.
322
323 A number of criteria for the sham diet were developed in order to ensure its integrity as a
324 placebo control for the low FODMAP diet. These criteria were developed as approach to
325 interpreting fundamental principles in the use of placebos (their similar presentation as the
326 intervention to facilitate blinding, physiologically inert with regards to the outcome of
327 interest), but specifically tailored to dietary intervention studies (Table 3). These criteria in
328 specific relation to the trial of the low FODMAP diet are: 1) to be a convincing exclusion diet
329 in order to encourage blinding that it is actually a placebo, 2) to contain a similar number of
330 specialist new products as the intervention diet, 3) to restrict an equivalent number of foods
331 compared with the low FODMAP diet, 4) to take the same amount of time for shopping and
332 involve the same level of adaptation when preparing meals as the intervention, 5) to take the
333 same amount of time and comprehension to teach as the intervention diet, 6) to be feasible to
334 follow, 7) to modify dietary carbohydrate sources (for ethical purposes patients were
335 informed that the unnamed active intervention diet involved altering carbohydrate intake),
336 and 8) to alter dietary intake but maintain FODMAP intake and 9) to not alter fibre intake,
337 which may impact on symptoms [50]. These criteria have been modified for application across
338 all types of dietary advice trials and although these generic criteria for design of a sham diet
339 have not been validated in trials, they provide practical approaches to facilitate blinding and
340 limit the physiological impact of the sham diet (Table 3).

341 The sham diet was designed following a systematic selection of foods to be included (suitable
342 foods) and excluded (unsuitable foods). Suitable and unsuitable food lists for the low
343 FODMAP diet were used as a starting point for creation of suitable and unsuitable food lists
344 for the sham diet, in order to create some restriction (criterion 3), whilst neither increasing
345 nor decreasing fructan (criterion 8) or fibre intake (criterion 9). Considering that many
346 exclusion diets alter grain intake, some grains were restricted to give the impression that the
347 sham diet was a true exclusion diet (criterion 1), to increase the burden of teaching (criterion
348 5) and following the sham diet (criterion 4), to focus the sham diet on carbohydrate intake (as
349 does the low FODMAP diet), which was referred to in the patient information sheet (criterion

7), and to necessitate the inclusion of new food products in the diet (criterion 2). Some regularly-consumed high FODMAP foods were allocated to the suitable list in order to maintain FODMAP intake during the sham diet (criterion 8). For example, approximately half of the fruits and vegetables considered suitable on the low FODMAP diet were assigned to the unsuitable list on the sham diet, and *vice versa* (criterion 3), whilst dairy products were allocated to the suitable list, to ensure lactose intake was maintained on the sham diet (criterion 8). Next, the habitual diet of individuals with IBS was examined from a previous study [13] and the top 10% of foods contributing to energy and carbohydrate intake were allocated as being suitable on the sham diet in order to promote feasibility (criterion 6) and maintenance of nutrient intake (criteria 8,9). Finally, the number of unsuitable foods on the sham diet was confirmed as being approximately equivalent to that of the low FODMAP diet (criterion 3).

Implementing and evaluating a sham diet

Dietary counselling in sham-controlled trials should be equivalent in duration for all participants, and ideally counselling should be provided to all participants by the same researcher. Access to written dietary resources has been associated with greater likelihood of response to lifestyle interventions [51]. Therefore if this type of information is to be provided, both intervention and sham diet groups should receive a similar level of written support i.e. the general format and length of the resources should be identical (criterion 5).

The evaluation of a sham diet should include assessment of its achievement of the criteria described in Table 3, and this can be achieved in a variety of ways. One approach is to undertake a pilot study whereby participants are advised to follow the sham diet and undertake a dietary assessment at baseline (habitual diet) and during the sham diet (criteria 8,9). An acceptability questionnaire can evaluate feasibility and other important outcomes (criterion 4, 6), as well as assessment of blinding (criterion 1). The sham diet can also be evaluated as part of the final RCT, and this can be undertaken both during the trial (i.e. an *a priori* interim analysis) and at the end of the trial (i.e. final analysis). If an interim analysis of a sham diet is undertaken, it should be performed late enough so that sufficient numbers can be included in the analysis but early enough in the case that the sham diet requires alteration. If changes to the sham diet are required this may require contact with the body providing ethical approval, and alterations should be carefully recorded and reported in the subsequent publication. In regards to the final analysis, evaluation of changes in dietary intake between

baseline and the sham diet and between sham and the intervention diet should be reported in any publication to confirm the placebo nature of the sham diet. Interim and final analyses must be conducted by an investigator who is blinded to the dietary allocation, in order to prevent researcher bias during dietary coding. Clearly, dietary assessment should use gold standard methods where possible.

Conclusions

High quality placebo-controlled evidence for food or dietary interventions is vital for verifying their role in optimising health or for the management of disease. This is especially important where the benefits of dietary intervention are coupled with potential safety implications such as compromising nutrient intake. The challenges with conducting placebo-controlled research in dietary trials are acknowledged. Sham diets are one approach of implementing placebo controls in dietary advice trials. Any new sham diet should be rigorously designed, implemented and tested as described. Feasibility, preservation of blinding, maintaining intake of the dietary component being investigated in the treatment group are major priorities when designing a sham diet which we propose can be addressed with careful consideration of the recommendations outlined.

Table 1: Glossary of terms relevant in dietary intervention trials

Term	Definition
Trials	
Dietary advice trial	A trial investigating the effect of dietary advice (written and/or verbal)
Food intervention trial	A trial investigating the effect of addition of a specific food into the diet
Nutrient intervention trial	A trial investigating the effect of addition of a nutrient into the diet, usually provided in the form of a supplement (e.g. capsule, liquid or powder)
Placebo-controlled trial	A trial incorporating a placebo control
Randomised controlled trial	A trial that randomly allocates participants to a control group or the treatment group
Uncontrolled trial	A trial that does not incorporate a control group. Paired changes between baseline and follow-up are evaluated to assess outcome.
Controls	
Active comparator control	A control group that receives an active intervention (e.g. standard therapy), usually used to determine whether the treatment under investigation is superior to standard therapy
Control	A group of participants not receiving the intervention that is compared with an intervention group, which enables comparison of the effect of the treatment
External control	A control group outside of the trial that is used to compare with the treatment group (e.g. data from medical records).
Feeding study control	Controlled study in which all food and fluid is provided to participants and in which the placebo group receive a diet designed bespoke for the purposes of the trial to be 'inert' in nature, and nutritionally matched to the intervention diet in all aspects except for the active component being investigated
No treatment control	A control group that do not receive a placebo or comparative intervention
Placebo control	A control group that receives an inert substance (e.g. sugar pill or saline) or sham advice/treatment
Re-supplementation control	Controlled study in which the same dietary advice is given to participants in both the intervention and control groups, followed by re-supplementation of the excluded food component to the placebo group
Sham diet control	Control whereby dietary advice is provided that modifies food intake without altering intake of nutrients or the specific food component being investigated
Bias, blinding, placebo	
Allocation bias	Bias resulting from a systematic difference between treatment and control groups in a trial, other than the intervention. This can largely be avoided by using randomisation.
Expectation bias	Bias resulting from the effect of participants' expectation of outcome (positive or negative)
Hawthorne effect	The effect of observation and/or measurement of research participants on outcomes
Observer bias	The inadvertent influence by the observer/researcher on participants
Placebo effect	Average improvement of a symptom or physiological condition following a placebo intervention in a RCT. The 'true' placebo effect is the effect after removing other contributing factors such as the natural course of the disease or spontaneous fluctuations
Selection bias	Selection of participants for inclusion in a research trial, or data analysis, such that it is not representative of the overall population
Subject bias	Bias resulting from participants behaving, or reporting to behave, in a way they think the researcher wants them to

Some definitions adapted from [1]

Table 2: Sham diet-controlled dietary advice RCTs

Reference	Treatment	Patient population	Study design/duration	Sham diet	Mode of advice
[38]	Exclusion diet removing foods based on presence of IgG antibodies specific to a panel of 113 food antigens	Migraine n=167	12-week single-blind parallel design RCT	Excluded same number of foods as proposed treatment diet (mean number of food per patient excluded not reported) Foods excluded did not provoke positive IgG antibody response and chosen based on difficulty of excluding foods from the true diet Success of blinding not reported	Verbal and written advice
[39]	Exclusion diet removing foods based on presence of IgG antibodies specific to a panel of 29 food antigens	Irritable bowel syndrome n=150	12-week double-blind parallel design RCT	Excluded same number of foods as proposed treatment diet (mean excluded foods per patient=6). Foods excluded did not provoke positive IgG antibody response and chosen based on difficulty of excluding foods from the true diet Success of blinding not reported	Verbal and written advice with access to a nutritional advisor throughout if required
[40]	Exclusion diet based on foods well tolerated according to clinical experience (rice, potato, lamb, bean, and peas)	Anal fissure n=161	8-week double-blind parallel design RCT	Elimination of foods reported as not tolerated by patients according to clinical experience (milk products, wheat, eggs, tomato, chocolate) Success of blinding not reported	Not reported
[41]	Nutrient dense low energy diet	Bulimia nervosa n=10	6-9 week single-blind, parallel design controlled trial Treatment group followed treatment diet for 6 weeks Control group followed 3-week sham diet followed by 6-week treatment diet	Based on baseline dietary preferences Success of blinding not reported	Written advice
[42]	Exclusion diet removing foods based on presence of IgG antibodies	Crohn's disease n=40	12-week double-blind parallel design RCT	Excluded same number of foods as proposed treatment diet (mean number of food per patient excluded not reported). Foods excluded did not provoke positive IgG	Written advice, recipes, menus and Access to a nutritional advisor throughout if

				antibody response and chosen based on difficulty of excluding foods from the true diet Success of blinding not reported	required
[43] abstract only	Exclusion diet excluding foods based on presence of highest IgG antibody response to four foods specific to a panel of 29 food antigens	Crohn's disease n=98	4-week double-blind parallel design RCT	Four foods with the lowest IgG4 titres excluded Success of blinding not reported	Written advice provided by a dietitian
[44]	Exclusion diet excluding foods high in microparticles (particulate silicates and titanium dioxide)	Crohn's disease n=83	16-week single-blind randomised 2x2 factorial trial	Foods containing sulphur dioxide and sulphites excluded Success of blinding not reported	Verbal and written advice provided by a dietitian
[45]	Exclusion diet excluding selected carbohydrate foods (low FODMAP diet)	Irritable bowel syndrome n=104	4-week single-blind randomised 2x2 factorial trial	Selected fruit, vegetables, grains excluded, with final number of foods equivalent to treatment diet Success of blinding not reported	Verbal and written advice provided by dietitian

Table 3: Important criteria for the development of a sham diet that may improve blinding and maintain the placebo nature of the diet

	Criteria	Rationale
Criterion 1	The content of the sham diet must give the impression it is the true intervention diet	To facilitate blinding
Criterion 2	If relevant, the content of the sham diet must require a similar number of specialist or 'new' foods compared with the intervention diet	To equalise the difficulty of the diet in order to facilitate blinding
Criterion 3	The sham diet must restrict or modify intake of an equivalent number of foods as the intervention diet	To equalise difficulty of the diet in order to facilitate blinding
Criterion 4	The burden of the sham diet should be equivalent to the intervention diet (e.g. time for shopping and cooking, level of adaptation required for preparing meals)	To equalise difficulty of the diet in order to facilitate blinding
Criterion 5	The sham diet takes the same amount of time to teach and requires same amount of comprehension as the intervention diet	To limit investigator bias and facilitate blinding
Criterion 6	The sham diet must be feasible to follow	To facilitate adherence
Criterion 7	The sham diet must modify dietary intake in a similar way to the intervention diet such that they can both be described in ethics documentation and information sheets without unblinding	To meet ethical requirements and to create a convincing placebo
Criterion 8	The sham diet must alter dietary intake but maintain intake of foods, food components or nutrients under investigation	To limit responses in the placebo group
Criterion 9	The sham diet must not alter intake of other foods, food components or nutrients that might impact on endpoints	To limit responses in the placebo group

Conflicts of interest: KW and MCL invented a mobile application to assist patients in following the low FODMAP diet

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