Table 3. Likely dissimilarities between food/nutrition and drug trials

	Food and nutrition trial	Drug trial
Form	Complex	Simple
Compliance	Low	High
Biochemical interaction		
Within components	High	Low
With other components	High	Low
Metabolism	Complex	Simple
Bioavailability	Low	High
Measurable outcomes	Low yield	High yield
Dose response	Shallow slope	Steep slope
Side effects	Low	High
Investigator workload	High	Low
Time for study	Long	Short

need to be taken into account. Problems associated with experimental population selection can be reduced by clearly defining the health issues or research questions, the priority population or high-risk group, the end-points or outcome measures, and the goals and targets. Investigators of a strictly defined trial may find that the size of the experimental population is too small to allow an adequate number of study subjects. This may be overcome by a multicentre approach. As in pharmacological trials, investigators of nutrition trials often find it difficult to obtain adequate information about the non-respondents. Whether or not characteristics of the study population match those of the non-respondents is an essential enquiry for results of an intervention to be generalizable to the experimental, and hence, reference population.[61] This may be overcome by collecting baseline or outcome data from all eligible individuals of the experimental population.[62] In order to eliminate bias in intervention allocation, randomization techniques are used.[63,64] There is a range of randomization techniques, specifically designed to answer defined research questions.[65]

Delivery of the intervention and assessment of compliance. Following randomization, trial investigators will intervene and monitor compliance. A nutrition intervention may be delivered by single or combined nutrient supplements,[66–69] nutrition education or counselling,[70–73] or food-based supplements.[74] The combination of all three intervention deliveries was adopted for the Australian Polyp Preventive Project, in which β-carotene (single nutrient) and a wheat bran (food-based) supplement, as well as fat reduction (nutrition counselling) were employed.[21] The use of various interventions needs to take into account study settings (therapeutic *vs* preventive), appropriate randomization techniques and, most importantly, the underlying research question and study objectives.

A more challenging aspect of a nutrition trial is the assessment of compliance. This is particularly relevant to intervention by way of an education program or counselling where the objective is to change a specific aspect of nutrient intake. Nutrition intervention means that study subjects take part in a prescribed regimen that aims to alter their nutritional status and, subsequently, health outcomes. The quality of end-points or outcomes depends on the degree to which nutrition intervention is maintained (compliance). Two factors known to affect compliance are the length of the trial period and the complexity of the study protocol (randomization and intervention delivery). Various strategies have been developed to enhance compliance.[75] In the Multiple Risk Factor Intervention Trial (MRFIT), it was found that nutrition intervention contributed to outcomes through both the continuing efforts of the nutrition counsellors and the level of dietary adherance.[76]

Ascertainment of quality end-points. Quality end-points in nutrition trials address efforts to achieve uniform ascertainment of outcomes from both intervention and comparison groups, and complete follow-up of study subjects over the trial period. In order to eliminate outcome observation bias, 'blinding' techniques (single or double) have been developed for drug trials. In nutrition trials where nutrition education or counselling may affect changes in other lifestyle factors, the use of single-blind or unblinded design is necessary. This raises several other issues which may also affect the quality of end-points. This includes possible unwillingness to stay in the prescribed nutrition regimen, over- or under-reporting the intervention to which the subject is prescribed, or unintended changes in background diet in intervention or comparison groups.

The completeness of follow-up of study subjects depends largely on the length of trial. Nutritional support (or therapeutic) trials are usually carried out in hospital and require short follow-up periods. In this setting, follow-up of all study subjects is easy for the entire trial period. A major cause of loss of follow-up is death. However, primary prevention trials often involve community groups or large cohorts, members of which are usually apparently healthy and not nutritionally depleted. These trials require many years of follow-up to observe study outcomes, usually the occurrence of disease or death. People are population-dynamic; they move, change jobs or names, and lose touch with the trial organization. As the length of trial period increases, the extent of complete follow-up of all study subjects decreases. The loss of follow-up can bias the effects of intervention on outcomes. For trials where mortality is an end-point, a national or state death register can be used to obtain the vital status of all study subjects.[77] It is now also usual trial practice to require subjects to provide the name, address and telephone number of a close relative or friend who may be contacted, in case of difficulty in follow-up.

Sample size

Sample size calculation in clinical trials relates to the ability to detect differences between intervention and comparison groups that are of clinical significance.[64] Sample size in clinical trials is thus an issue of statistical power. Generally, the calculation is on the basis of comparison of a single mean with a standard or a comparison of two means.[78] However, where the confidence in a trend or relationship is sought, the statistic of the intercept or slope of the line is what must be considered, with the number of points on the line improving the power. Intercepts or slopes may be compared.

If the underlying differences between the intervention and comparison groups are affected by compliance and quality of end-points, the sample size will need to be larger.

Accumulation of adequate end-points. A high-risk population approach ensures accumulation of a sufficient number

of end-points. Nutrition support trials enrol almost exclusively high-risk individuals and require relatively small numbers of study subjects to achieve clinical significance between experimental groups. Using as few as 34 patients with alcoholic hepatitis, Simon and Galambos were able to demonstrate that peripheral parenteral nutrition compared with standard therapy rapidly improved liver function and morbidity.[79] Large scale prevention trials also rely on a high-risk population approach to minimize the spread (variance) of end-points and, hence, improve statistical power. This is equivalent to the use of entry criteria to establish an experimental population. A common high-risk approach is to set an age limit. A suitable duration of follow-up can influence quality of end-points as well as accumulation of adequate end-points. More importantly, an inadequate trial period can decrease the power of statistical tests.

Effect of compliance. Poor compliance can result in similarity between the intervention and comparison groups, and decrease the ability to detect the true difference. Additionally, poor compliance can introduce bias that results in increased variance in intervention or comparison groups and, hence, the decreased power of tests.

Food and nutrient database management

Database management and statistical analyses are important considerations in all clinical or intervention trials. In nutrition trials, particularly those involving education programs or counselling, food and nutrient intake data management and analyses are generally necessary. Food intake data are first collected and then converted into nutrients. There is nutrient conversion software such as Nutritionist-III (N-Squared Computing, Salem, OR, USA) and Diet/1 (Xyris Software (Australia), Queensland, Australia) that allows the direct conversion of food to nutrient intakes. They depend on various food comparison tables which need to be defined. The ability to incorporate food and nutrient with non-nutrient data in the statistical analyses is becoming of increasing interest. For investigators who do not have access to nutrient conversion software, database management software can be used. Food intake data are stored, preferably in a computer, in the form in which they are collected. This allows each food or beverage to be averaged as daily intake per gram, and grouped for later use. The preservation of intake data in relation to time of day, day of week, or season is increasingly required.

Where more than one source of food composition tables is required, it is necessary to cross-check nutrients and measurement units. A new food composition database may be generated if relevant to the study population but will require description and definition in any report.

Background diet

A special feature of nutrition trials is the background diet, or non-intervention dietary intake. Community intervention (primary prevention) trials where the dietary goal is to reduce or increase specific nutrients can result in concomitant changes in background diet. In the MRFIT, the dietary goals were to progressively reduce fat intake as energy by 10% (from 35 to 25%), saturated fat as energy by 3% (from 8 to 5%), and dietary cholesterol by 150 mg per day (from 250 to 100 mg/day), with the energy adjusted to achieve 1.15 times the ideal body weight.[70] In order to achieve these dietary goals, recommended food consumption patterns were designed to take into account existing food patterns and how food permeates daily living. In this trial, the intervention group underwent minimal changes at the beginning of the trial in their usual eating pattern, and then progressively moved to the study dietary goals. The ability to control background diet (and reference diet) in accordance with the nutrition intervention goals can provide participants with an incentive for dietary adherence, and allow the investigators to assess more accurately the effects of intervention.

Nutrition assessment

Measurement errors inherent in nutrition assessment methods, particularly dietary assessment, raise important methodological issues for all such nutrition studies, including nutrition intervention trials. The problem with diet is the lack of gold standard reference methodology. Validation is provided in part by a consideration of how sensible the energy intake in relation to BMR, by biochemical checks such as urinary nitrogen excretion, protein intake, and 'fingerprinting of plasma phytochemicals in relation to intake, along with prediction of outcome'.[22]

Anthropometry, laboratory (e.g. body composition, biochemical tests and functional tests) or clinical methods can be used to assess nutritional status that cannot be otherwise adequately assessed by dietary means.

Limitations of food or nutrition trials

Age dependency

The importance of early life nutrition on later life health is increasingly understood.[80–82] Ideally, clinical trials for the aged would begin early in life, but this is not practical. The next best strategy is for trials to be undertaken in age segments and then the findings pooled across the life span in much the same way as is done for life expectancy tables at birth. The limitation is that the deductions may not always be valid.

Major community-based intervention studies should now seek to reserve genetic and biological material so that subsequent generations of investigators might take advantage of earlier research programs.

The use of single food or nutrients in trials and their interaction with other nutrients

Univariate, reductionist scientific methodology usually prevails in clinical trials but the findings from such trials have limited applicability. Design which acknowledges the multivariate nature of food, food habits and food effects will, in general, be superior. However, even here, the cooperativity, synergistic, additive and confounding effects of various food components will need to be acknowledged.

Appropriateness of extrapolation of results from a trial setting to the broader population in various clinical situations

Representativeness. There is a tendency for clinical trials to be carried out in non-representative populations and, while they are valid in regard to that particular population, they may not be valid for a representative population or another group of individuals. Increasingly, it could be argued that

clinical trials ought to be carried out in samples representative of the population for which the findings are intended.

Adherence and compliance. Nutritional intervention requires various periods of time before beneficial effects become evident. Longer studies affect patient compliance. In addition, the form of nutritional intervention, whether food (i.e. functional food) or formula feeds (i.e. elemental diets), may not be sufficiently palatable or interesting to gain adherence to the regimen. Again, extrapolation of results to a less supervised free-living setting may be difficult.

Confounding factors. Lifestyle, food habits and health status are inseparable. The ability of health-care providers to understand the food culture of patients and wider society is crucial in order to avoid misapplication of advice based on a clinical trial. For example, fish, which is rich in ω-3 fatty acids, consumed two times per week is likely to prove beneficial as far as certain cardiovascular risk factors are concerned.[83–87] However, the cooking habits practised by certain cultures (e.g. the Chinese tendency to add soy sauce to fish dishes) might negate the putative beneficial effects by increasing sodium intake.[88]

Limits to extrapolation from cross-sectional studies. The clinical trial helps to ensure that deductions from cross-sectional studies have cause and effect validity. Many cross-sectional studies on food, nutrition and health are available; most of them are population-based studies which provide an operational case for a possibly useful intervention. These cross-sectional situations allow it to be seen that different nutritional pathogeneses may operate for the same disease outcome in different ethnic groups (e.g. selenium deficiency cardiomyopathy in China,[89] or cobalt excess cardiomyopathy in Europe).[90,91]

Inefficiencies in intervention investment and the nature of meaningful outcome measures. As well as health costs and benefits, the economic and environmental costs and benefits of interventions need to be taken into account. Increasingly, the considerations are economic but rarely ecological.

Intermediate changes versus ultimate morbidity and mortality outcomes. It is often of particular investigatory value to seize upon intermediates in the pathway between food and disease or death as achievable outcome measures. However, like the requirement with age-related outcomes, the various steps in the nutrition–health pathway require amalgamation and even this deductive and synthetic logical process does not always fulfil expectations.

Ethical issues

There are a number of unique ethical issues relating to nutrition, as follows: (i) the issue of prevention; (ii) the issue of the individual's right to be fed, which relates to the long-term poorly identifiable effects of change in diet and the unintended consequences on background diet; (iii) the issue of disruption of food-cultural tradition and its associated belief systems; and (iv) issues which impact on the overall security of the food supply and its sustainability.[25,92]

In summary, the design and conduct of a clinical trials in nutrition are more demanding than the corresponding drug trials, although the need for such trials will rapidly grow.

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