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# Evaluating the effects of food on health in a world of evolving operational challenges

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ABSTRACT

In a context of rising interest in food and supplement clinical trials, operational considerations for the set-up and conduct of these research projects remain difficult to address in the absence of a harmonized referential. Food trials tend to be more pragmatic than drug trials which are usually more elucidatory. However, comparing them is difficult because the objectives they serve are different. Food trials are usually conducted to evaluate the effect of food products on the prevention or mitigation of symptoms, not the treatment or cure of a condition. In this article we explain these main differences and discuss several key operational and regulatory aspects to consider when dealing with clinical research evaluating the effect of food products on health-related biomedical or behavioral outcomes.

## 1. Introduction

When has the association between health and food been described and evaluated for the first time? According to written history, this association was stated in ancient Greece by Hippocratic writers at a time when no clear-cut was available to distinguish food from medicinal products [1]. While clinical research is often associated to the development of medicinal products, it should be emphasized that one of the first reported, prospective, controlled, parallel-arm human experiment was conducted to evaluate the effect of food interventions on health: In 1747, when Captain James Lind's crewmembers died of scurvy on His Majesty's Ship *Salisbury*, he tested different food supplementations (along with standard meals) in groups of sailors, and reported that the group eating lemons and oranges shown signs of recovery. Citrus were later used for the prevention of scurvy among European sailors [2]. More recently, consumer trends evolved throughout the 20th century: While new consumer habits appeared along with globalization, malnutrition remains a worldwide health concern. A sign of the political & societal awareness of the association between health and food is the long-standing collaboration between the World Health Organization (WHO) and Food and Agriculture Organization (FAO) of the United Nations, which led to the foundation of the *Codex Alimentarius* in 1963 [3]. Today, health-conscious consumers continue to express a need for transparency and for the development of new products [4]. These are some of the reasons why the effects of food products on health are studied by conducting clinical trials designed to evaluate and understand their effect. These trials share many methodological and organizational aspects with trials conducted for the development of pharmaceutical and biotechnology products: Indeed, according to the WHO, food clinical trials *should be governed by standards of safety, quality and efficacy that are equivalent to those required for other pharmaceutical products* [5]. However, several operational and regulatory challenges which are specific to this niche area are presented in this article.

## 2. Defining clinical research on food

A common difficulty in defining clinical research on food relies in the definition of the tested intervention itself. A clinical trial designed to evaluate the nutritional effects of a diet, a whole food or its nutrients should be referred as a *nutrition trial* or a *conventional food trial*. Also, a food intervention may be tested to evaluate a physiological response or the prevention of symptoms or chronic conditions: In case the effect of a tested intervention goes *beyond basic nutritional functions*, it can be referred as *functional food*, despite the absence of a single, universally accepted definition [6].

Clinical research professionals managing food clinical trials are often tempted to compare their methods to those needed for pharmaceutical product development. Food and pharmaceutical trials share a lot of organizational aspects, but comparing *how* they are conducted may be the source of misconceptions because the main differences rely in the reasons *why* they are designed [7]. Drug clinical trials follow a

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typical series of phases before and after market approval, a process that is not relevant for food products. Clinical studies on food are however needed to investigate and better understand their effect on the prevention or mitigation of symptoms rather than the treatment of a condition. Therefore, relevant clinical development plans are needed to provide the needed demonstration to substantiate a claimed effect. Food trials objectives, especially in early development phases, tend to be more exploratory by nature for both scientific and organizational reasons:

- Firstly, the effects of food products on health rely on multiple factors, which need to be studied to better understand their mechanisms of action. We are used to identify bulk actives of a pharmaceutical drug, as they are selected for their specific target while other compounds (i.e. excipients), which serve as vehicle for actives, are ideally inorganic and/or should be as neutral as possible [8]. However, active ingredients of a food product and other ingredients (i.e. matrix) can interfere with each other, act on multiple targets, and vary over time, making the assessment of mechanisms of action of each ingredients complex once ingested, as explained by de Vos et al. in 2006 when addressing the concept of nutridynamics [9].
- Furthermore, many parameters must be considered when conducting a food trial: Whereas physical activity, sleep and smoking are monitored among other relevant parameters, food and fluid intake, as well as diet habits, are important to collect in all participants as their background diet may interfere with the effect of a tested food intervention.

These aspects eventually impact the number of clinical assessments and the volume of data that is needed for a food trial (*see below figure*), while the effects of food products remain subtle when compared to medicinal products. It should be emphasized that the participant burden associated with this number of assessments may seem important for trials that do not bear high risks associated to the tested product consumption [10,11]. This impact should not be underestimated while innovative tools for data collection are being specifically designed for clinical study participants, requiring their involvement daily (see Fig. 1).

## 3. General considerations for the management of food clinical trials

### 3.1. Study design

From a methodological point of view, the main challenges for the conduct of food trials are dealing with the evaluation of subjects' history and baseline characteristics (which should include diet habits as well as the usual demography, concomitant medication and medical history parameters) as well as the form of the tested intervention. In both pharmaceutical and food trials, wash-out periods may be applied before allocation of an intervention. However, an additional focus may be needed when testing a food product as it may already be marketed and easily accessible, as compared to an Investigational New Drug (IND). Another methodological aspect to consider is the blinding, which is another challenge in placebo-controlled studies, especially if the tested intervention has a specific taste, texture, aroma or appearance as explained by Yao et al. in 2013 [12].

Also, one important topic is the way to cope with the rather small effect of interventions (as compared to pharmaceutical products) in food studies which are, as explained above, more exploratory by nature and often focused on the prevention or mitigation of symptoms. When a specific model is needed to evaluate the effect of a food intervention (i.e. selection of subjects who are at risk to develop specific symptoms) one must consider criteria to stop the study if the occurrence of symptoms is too low, preventing the assessment of product effect according to protocol criteria. Research teams are therefore encouraged to define stopping rules using state of the art methodology: Considering interim analyses with futility stopping rules is a good way of validating hypotheses and avoid the recruitment of too many participants (and optimize study budget, resources and recruitment plan). These rules are needed for pharmaceutical trials for both safety and efficacy reasons, but only the latter is usually considered in food trials given the relative safety of food products [10,11].

### 3.2. Trial set-up

As for the management of trials evaluating INDs, food trials require qualified experienced investigators teams, who are also used to deal with specific features: To capture additional data dealing with

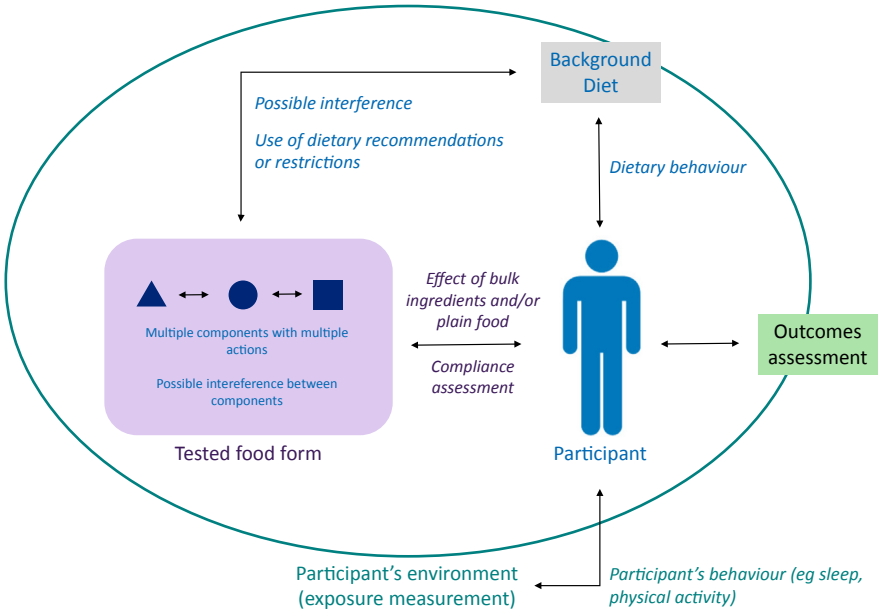


**Fig. 1.** Considerations for the evaluation of the effect of a tested food in clinical setting.

participants' environment (e.g. diet, physical activity) the involvement of additional disciplines, as study dieticians, is expected. This should be considered by sponsors (during site feasibility assessments) and investigators (for the recruitment of appropriate subjects, and to manage the subject time at site). Site selection and recruitment of participants represent the main bottlenecks for the management of clinical trials as they may impact both study timelines and budget. To avoid these pitfalls, a specific focus on the number of countries and sites is needed for food trials, for several reasons. Firstly, international food trials are usually avoided because the heterogeneity in diet habits across countries may be the source of unwanted additional inter-subject variability. Furthermore, the rather healthy status of volunteers that are enrolled in food trials (when maintenance of a healthy status of prevention of risk is studied), has an impact on the risk–benefit ratio. To facilitate enrolment and avoid drop-outs, sponsors tend to conduct food trials in a limited number of investigative sites where an important number of participants can be included. Conducting a study in a limited number of sites is even more important for sponsors evaluating fresh products: The rather short stability of the tested food interventions, which require continuous manufacturing and shipment of the investigational products (IPs), eventually impacts the operational complexity and cost of the research.

Monitoring both participant's diet and compliance with IP intake represent key challenges in food clinical studies. Indeed, these must be considered for multiple reasons:

- As explained above, the background diet may interfere with the effect of the tested products, which is the reason why dietary restrictions may be applied throughout subjects' participation [12]. Also, knowing participants' baseline diet habits is needed to ensure that any modification to these habits are appropriately accounted for as they may have an impact on the product effect criteria. To collect this data, (either prospectively or retrospectively), research teams rely on robust questionnaires (such as dietary recalls or food frequency questionnaires) which should be carefully chosen with a clinical study dietician according to the clinical study needs. This should also be selected by considering the time to complete these questionnaires, as they might have an impact on subject burden [13]. The recent surge in mobile health technologies should however facilitate the prospective record of clinical study participant's diet.
- To calculate compliance with IP intake, return and assessment of used/unused product doses during evaluation visits is recommended. When associated to a participant's diary, assessment of compliance with IP intake should not be different from a pharmaceutical trial's one. However, if the return of the study products is not possible (e.g. portions to be prepared and consumed by the participants at home, for which packaging is easily thrown away by participants), research teams rely on participant's diary even more to calculate compliance with product intake. Investigators are encouraged to reconcile this after an interview with their patients during evaluation visits.

### 3.3. Regulatory framework

Some regulatory aspects require attention when setting up clinical trials on food: Even though risks associated to food IP consumption are usually low because these products may be considered as safe [10,11], the way to obtain an authorization to conduct such a study vary across countries. Identify which competent authority is responsible for approving the conduct of a food trial can be difficult because participants' risks go beyond the IP intake, as they also depend on the protocol procedures and the frequency of the participants' visits:

- In several countries, the need to obtain approval from a competent authority (CA) may depend on the nature of the tested product (Authorization from CA may be needed for a tested drug, and not needed for a tested food).
- In others, the need for competent authority application may be triggered by the risks associated to the study design (i.e. models, procedures or products associated to protocols).

Sponsors are therefore invited to perform a deep assessment of country specific regulations and guidance issued by authorities. However, country-specific guidance is not always clear about food clinical trials, which may end up in a grey zone between interventional and non-interventional research. Furthermore, investigating the health benefits of a food may bear the risk to requalify the tested food intervention as an IND [14]. The regulatory landscape and availability of clear guidelines for the management of food trials can therefore be a key differentiator in the choice of study countries by the sponsors, and has a positive impact on their attractiveness. This is even more important when a clinical trial intervention must be defined: Participants' diet may also be collected and monitored when behavior change is evaluated as a clinical study endpoint to assess the effect of behavior change techniques (e.g. providing feedback or guidance on participant's behavior, or changing the participant's environment) [15]. According to the NIH, studies evaluating the outcome of such behavior change techniques now qualify as clinical trials [16].

Another operational issue for sponsors of food trial is the lack of a dedicated international referential for their execution even though working groups have been addressing this question already [17]. As explained by Schmitt et al. in 2012 [18] the use of ICH Good Clinical Practices (GCP) is relevant to ensure a high quality by design and a proper execution of food trials. However, the purpose if the ICH being the *harmonisation of technical requirements for registration of pharmaceuticals for human use* [19], specific language cannot be applied for food trials, including:

- the definition of IP relating to a *pharmaceutical form,*
- the definition of Adverse Event relating to *pharmaceutical product* or *medicinal product*,
- the content of the Investigator's Brochure [20] or the lack of information on *pharmacokinetics* and *pharmacodynamics* [21] which may not be applicable.

Sponsors of clinical studies evaluating food products therefore need to rely on adequate definitions in their study documentation (including Clinical Study Protocol and Investigator's Brochure) to cope with the lack of an international referential that could be used in medical research, whatever the nature of the IP. To ensure the scientific validity of food trials, sponsors must comply with requirements that are otherwise needed for the conduct of drug trials (including and not limited to the use of state of the art methodology, an adequate Quality Management System, suitable manufacturing practices and relevant investigational product analyses) despite a universally accepted referential for conducting food trials.

## 4. How to embrace changes

In 2017 the ICH released a reflection paper on *GCP renovation* [22], aiming to modernize ICH E8 [21] and renovate ICH E6 [20]. To renovate the guideline E6, the ICH suggests the use of a set of three appendices to describe traditional clinical study designs but also designs that cover broader research questions and alternative types of data sources commonly referred as data from the "Real-World". As the ICH requested feedback from stakeholders, sponsors involved in the clinical development of food products should take this opportunity, as well as further public consultations from the ICH, to address the challenges that are described above. That way, ICH-GCP may be a referential that could be applicable either for pharmaceutical products or other products, including food. There is now a need to have standards updated to take

them into account whatever the type of intervention. As clinical research professionals, research participants are at the center of our concerns: The principles established in ICH guidelines, focused on subject rights and integrity, and quality of clinical trials should be compatible whatever the objectives of the research involving human participants. We therefore believe that an international referential applicable for all types of IPs would be in the interest of participants, investigators and sponsors.

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