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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

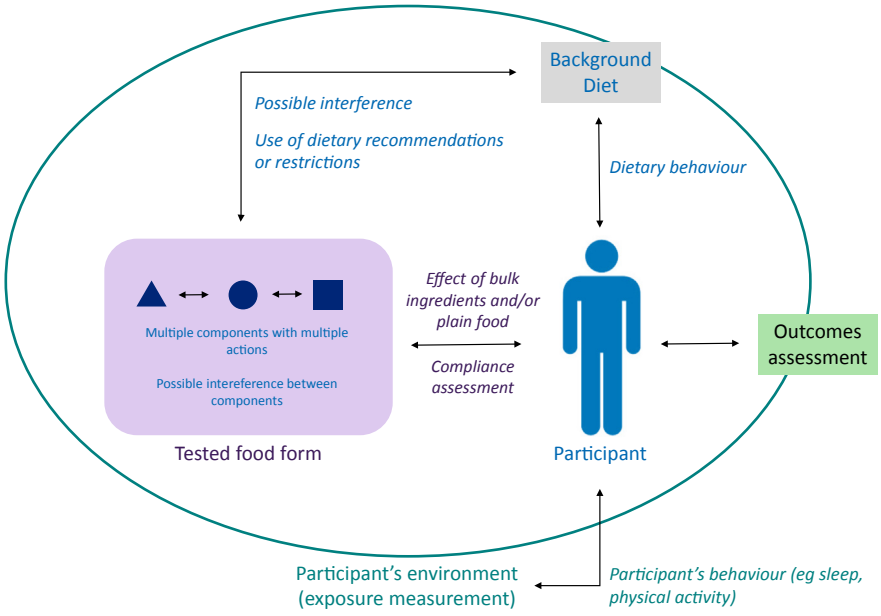

Fig. 1. Considerations for the evaluation of the effect of a tested food in clinical setting.