Progress in Lipid Research 65 (2017) 1–11

Contents lists available at ScienceDirect

Progress in Lipid Research

journal homepage: www.elsevier.com/locate/plipres

Review

Best practices for design and implementation of human clinical trials studying dietary oils

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ARTICLE INFO

Article history:
Received 3 September 2016
Accepted 24 October 2016
Available online 26 October 2016

ABSTRACT

Dietary oils are a significant contributor to overall energy and fatty acid intakes. Changes in the amount and/or type of dietary oils consumed have the potential to impact human health. Clinical trials represent the gold standard for testing the health impacts of such changes in dietary oils. The objective of this review is to explore best practices for clinical trials examining impacts of dietary oils including 1) pre-clinical topics such as research question generation, study design, participant population, outcome measures and intervention product selection and/or preparation; 2) clinical trial implementation topics such as recruitment, trial management, record keeping and compliance monitoring; and 3) post-clinical trial topics dealing with sample analysis and storage as well as management, publication and data access. The use of digital case report forms, and the best practices in reporting and publishing results are also addressed. In summary, properly designed and implemented clinical trials studying dietary oils produce strong scientific evidence-guiding their use.

Contents

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http://dx.doi.org/10.1016/j.plipres.2016.10.003
0163-7827/

1. Introduction

Dietary fats and oils exist as an important contributor to total energy intake and continue to be explored in relation to almost every aspect of human health, especially chronic diseases such as cardiovascular disease. Dietary oils significantly contribute to overall fat and fatty acid (FA) intake in many populations, including Canada and the United States, where they provide well over 20% of dietary energy [1]. Novel dietary oils, which are being created with specific FA profiles, possess the potential to modify current FA intakes more substantially than is possible with conventional oils [2–4]. Indeed, modifying the FA profile in a novel dietary oil can profoundly impact health. Randomized, controlled trials (RCTs) are considered to be the "gold standard" in clinical nutrition research [5] since RCTs allow for investigation and establishment of cause and effect relationships between interventions and outcomes. Thus, appropriately designed, conducted, and reported RCTs are key to determining the impact of dietary oils on human health.

The objective of this review is to explore best practices for clinical trials using dietary oils including 1) pre-clinical topics such as research question generation, study design, participant population, outcome measures and intervention product selection and/or preparation; 2) clinical trial implementation topics such as recruitment, trial management, record keeping and compliance monitoring; and 3) post-clinical trial topics dealing with sample analysis and storage as well as management, publication and data access. The goal is to highlight unique considerations related to conducting clinical trials using dietary oils through each section.

2. Pre-clinical stage

2.1. Research question and hypothesis

Clinical trials involving dietary oils represent prospectively planned research studies designed to answer specific questions regarding the impact of modifying the FA, or other lipid, content in a diet through the use of dietary oils varying in composition. Therefore, the critical first step in a clinical trial is establishing the research question which the trial will strive to answer. The research question should be precise and clearly defined as it will directly influence all other aspects of the trial, including the design, duration, eligibility criteria, test product and the control [6]. A clinical trial should include a clearly stated specific objective and hypothesis which is related to the research question and a particular outcome or endpoint.

In clinical trials with dietary oils, research questions may relate to any component of the dietary oil, or the way that inclusion of the oil into a diet modifies an outcome. Typically, the overall amount and/or composition of FAs in a diet are of interest, however, sometimes non-FA components, such as phytosterols or fat soluble vitamins found in oils may form the basis of the research question.

2.2. Selection of primary and other outcome measures

Clinical trials typically have one primary objective and outcome, thus additional objectives, or outcomes which are measured, would be secondary. Objectives or outcomes measured after the trial has been completed would be considered tertiary or exploratory. Classification of outcomes is also critical as a way to deal with multiplicity [7], the testing of multiple comparisons, "outcome switching" [8], and to avoid data-dredging which can lead to unreplicable results [9]. A finding related to the primary outcome of a trial, upon which the trial was designed and powered in an a priori fashion is stronger evidence than secondary, tertiary or exploratory findings.

The selection of the right primary outcome is critical to the success of a clinical trial. Primary outcomes should be explicitly defined and relevant to the research question. Outcomes which are of the most value are clinical endpoints, which are characteristics or variables measured in trial participants that reflect how they feel, function or survive [10]. Alternatively, and most common in clinical trials involving dietary oils, are surrogate or intermediate endpoints. Surrogate measures are intended to substitute for clinical endpoints, often to reduce the cost, sample size and completion time of clinical trials [11,12]. These surrogate endpoints should have a proven relationship with the clinical endpoint of interest, such as a strong biological link to the disease of interest demonstrated through basic research and mechanistic trials in humans, or a strong and demonstrated ability to be predictive of a clinical endpoint [10,12–14]. Analytical procedures and methods for the primary outcomes should also be well defined and reproducible [5,13,15].

In addition to research outcomes, outcomes related to compliance or adverse events should also be considered in the planning of clinical trials [5,6,16]. An adverse event is any unexpected and unfavorable medical occurrence temporarily associated with a clinical trial treatment, regardless of whether it is caused by the treatment or not. Biomarkers of dietary oil intake can be the fatty acids being investigated, or their metabolites, in blood, tissue, or feces. In trials where the dietary fat intake is being modified, outcomes such as plasma, red blood cell, or adipose tissue fatty acids may be appropriate compliance outcomes. The use of fatty acid composition as a marker of dietary intake has been reviewed extensively by Hodson et al. [17]. In clinical trials where dietary oils that contain phytosterols are being fed, the shift over time in phytosterol concentrations in the plasma can be utilized to monitor compliance. However, circulating phytosterol concentrations suffer from significant inter-individual variability in metabolism which may be unrelated to compliance [18]. Finally specific markers can be added to the dietary treatments, such as para-aminobenzoic acid which can be measured in urine, and then quantified to assess compliance [5,16]. Additionally, participant completed logs, diaries, or questionnaires, and exit questionnaires about compliance can be considered as useful compliance indicators [19].

Adverse event outcomes should generally be identified in a clinical trial. These typically include basic clinical chemistry as well as hematological measures. Adverse event outcomes help to detect any potential negative health effects of a treatment which may not necessarily be seen in the other measures. These negative health effects could range from very minor symptoms to serious health complications [5,20]. Monitoring and recording of adverse events is important because not all potential outcomes of a treatment may be known in advance and may differ between participants. Once recorded, data on adverse events can be used to determine the relationship between the treatment and adverse event, on a scale from unrelated to the treatment to definitely related to the treatment [20]. In addition to these objective measures