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Clinical trials using functional foods provide unique challenges

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ABSTRACT

Clinical trials usually evaluate medicines as the intervention of choice to improve health. Changing the intervention to a functional food would appear straightforward, but there are many unique technical issues that will confront the Principal Investigator and research team. These challenges are found in each of the three distinct phases of a trial: the initial organisation of the trial, running the trial, and finally, the dissemination of the data following successful completion of the trial. Each challenge presents very different issues that will limit the conclusions of the trial unless addressed properly. We suggest that careful planning of the trial taking into consideration thirteen important technical parameters can ensure that the data are relevant and lead to reliable conclusions, every bit as valuable as those obtained in trials with medicines.

1. Introduction

The proof of effectiveness of medicines now relies on clinical trials, although the treatment of illnesses by medicines has been based on anecdotes and transmitted experiences for thousands of years. Most clinical trials test medicines that are pure synthetic compounds, possibly derived from natural products, that are commonly referred to as drugs. This emphasis on medicines in clinical trials relies on two widespread rationalisations that medicines are effective in treating disease, and that pharmaceutical companies provide sufficient funds to test medicines. However, trials to define whether functional foods, understood as foods that can alter disease in addition to providing nutrition (Brown, Poudyal, & Panchal, 2015), can be the intervention of choice are becoming more and more common. Functional foods have been used for centuries to prevent disease throughout the world, but their use in treating disease is gaining more and more appeal, especially when used in conjunction with current pharmacological approaches or even as a replacement for drug therapy. Functional foods are often referred to as “natural health products” or “health foods”. Functional foods appear as conventional foods that we would eat, such as muffins or snack bars, but provide health benefits in disease conditions because of their content of a specific bio-ingredient. The FlaxPAD trial and the HyperFlax trial are examples of recent clinical trials that use different functional foods containing milled flax as their interventions (Caligiuri, Penner, & Pierce, 2014; Rodriguez-Leyva et al., 2013).

2. Setting up the trial

The path to successful clinical trials with functional foods usually begins with obtaining relevant background evidence from basic science and discovery-based research. However, clinical trials can be justified on the basis of epidemiological, testimonial or anecdotal evidence as well. Long term historic use of a compound for a particular ailment can be another powerful justification for initiating a functional food trial. Our personal journey to the start of our first major double-blinded, placebo-controlled, randomised trial, the FlaxPAD trial (Rodriguez-Leyva et al., 2013), was no exception. We reported positive data in cardiovascular disease models in rabbits and mice demonstrating anti-arrhythmic, anti-atherogenic and anti-inflammatory actions of dietary flaxseed (Ander et al., 2004, 2010; Bassett et al., 2011; Dupasquier et al., 2006; Dupasquier et al., 2007). The generation of many peer-reviewed publications documenting the potential of dietary flaxseed to improve cardiovascular disease was critical to justify a long, expensive clinical trial.

Even with these publications on animal models of cardiovascular disease, the data were insufficient to justify the launch of a major trial investigating the effects of flaxseed in a diseased human population. Pilot studies were necessary in healthy people to demonstrate that they could eat foods that contained the necessary doses of flaxseed for extended periods of time, to ensure the food was safe and to determine if characteristics of the population to be studied in the major trial could receive the bioactives in flaxseed that were proposed to provide the

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health-related benefits. These studies were successful and the results were published to support the feasibility of the final FlaxPAD trial (Aliani, Ryland, & Pierce, 2011, 2012; Austria et al., 2008; Kaul et al., 2008; Patenaude et al., 2009; Rodriguez-Leyva et al., 2011; Caligiuri, Penner, & Pierce, 2014).

This discussion provides information on the pathway necessary to ensure the success and feasibility of a major interventional clinical trial on flax and also demonstrates the length of time it takes to carry out this work. In overview, the animal work was started in 2001, the trials in healthy humans started in 2005, and ethics and regulatory approvals were gained from Health Canada, St Boniface Hospital in Winnipeg and the University of Manitoba in 2007/08. It was then that the trial was placed on clinicaltrials.gov. In 2008, patient recruitment began but it was only completed when 110 patients were enrolled in 2010. The FlaxPAD trial had a one year duration so the data collection was completed in 2011. Like any trial, it took a much longer period of time beyond the one-year duration of the actual trial to collect data from patients in the trial. Data analysis takes many more years. Data from this trial continue to be published 5 years after the last patient finished the study (Caligiuri, Aukema, Ravandi, Guzman, et al., 2014, Caligiuri, Aukema, Ravandi, & Pierce, 2014; Caligiuri et al., 2016; Edel, Aliani, & Pierce, 2015; Edel et al., 2016; Edel, Rodriguez-Leyva et al, 2015).

3. The challenges

It is a major challenge to carry out clinical trials on functional foods in a diseased population. To begin with, obtaining funding through competitive grants is increasingly difficult as success rates fall. Contract funding support through the drug industry is becoming increasingly scarce as well. The movement of large numbers of clinical trials to India and China due to lower operating costs and large populations in these countries has resulted in fewer opportunities to carry out trials in North America and Europe, the traditional homes for most medicines-based clinical trials. Government regulatory bodies, hospital and university ethics review panels and health safety agencies in every country are requiring more standards to be met, not less. Further, demands from journal reviewers for more stringent controls of trials including double-blinded, randomised, placebo-controlled, wash-out, cross-over, longer trials, increasing numbers of patients enrolled in the trial with more complex inclusion and exclusion criteria have become the norm. This has increased the complexity and costs of running a trial. Each of these challenges must be overcome if the trial is to produce timely data of use to the sponsor, the scientific community and, ultimately, the public who will benefit from this information.

Functional foods offer unique challenges to the investigators who carry out these trials. Although trials with natural health products can be more complicated to run than a conventional drug trial, these trials may become more common as science searches for comprehensive and effective approaches to complex disease processes. A Principal Investigator and research team proposing their first trial in this area may not be aware of some of these added difficulties as they embark in such a direction. The purpose of this article is to identify some of the unique challenges that a clinical investigator will likely face when undertaking a trial in a diseased population using a functional food as a therapeutic intervention, and offer some ideas on solutions.

We have identified a number of specific problems to be addressed and overcome in these types of trials if the results are to be reliable, reproducible and endorsed by the scientific community as well as the lay public (Table 1) (Pierce, 2012). These challenges will be presented to the trial's Principal Investigator and research team at all three distinct phases of a trial: the initial organisation of the trial, data collection and completion of the trial, and the publishing of the data obtained from the trial.

Table 1
The unique challenges of a nutraceutical/functional food trial as opposed to conventional drug trials.

1. More difficult to get industrial funding to support the trial
2. Technical support to initiate a trial can be non-existent
3. The placebo is more challenging to create
4. Food is difficult to deliver to patients
5. Foods need to be maintained in a fresh state
6. Tasty food is an issue – tasty drugs are not
7. Patients can gain access to foods easier than drugs
8. Patients can share their food
9. Conventional compliancy markers can be unreliable
10. Plasma biomarkers of compliancy must be unique to the food/nutraceutical intervention
11. Statistical analysis
12. The response of the public to positive results
13. Healthy skepticism (disbelief?) of the results from the medical field

4. The organisation of the trial

Challenge #1 Obtaining adequate funding support

In drug-based clinical trials, the sponsor is usually industry. A pharmaceutical company will finance a trial to advance knowledge about a unique drug when they have patenting protection and commercialisation opportunities. A major investment of capital in the clinical trial is reasonable when there are financial gains to be made with the drug. Natural health products, especially functional foods, do not usually have this sort of ultimate gain that justifies a large financial investment in the form of a clinical trial. As an example, bagels containing therapeutic doses of unrefined flaxseed (Aliani et al., 2012) cannot be patented. Since composition, process and indication patents have been awarded for functional foods ingredients, specific derivatives or groupings of the constituents of flaxseed could be patented, but the extra costs involved in producing and patenting these products would likely make them unviable as ingredients. Commercialisation of food products containing unrefined flaxseed can generate significant revenues but no single company could protect these products for their financial benefit alone, as occurs with a patented drug. This makes it unusually difficult to identify sponsors who may support the initiation of such a trial.

If support from industry is not possible, using competitive grant support to finance a trial may be the only alternative. However, this usually entails persuading a conventional panel of medical reviewers of the validity of this trial. This can be a difficult proposition in view of the concerns identified below. The exceptions to this can be found in specific panels such as the Complementary Medicine panel at NIH where the concept of functional foods having the capacity to alter disease progression is already accepted. The Australian Government is supporting university-industry collaborations, including biotechnology and biomedical science, with funding through Innovation Connections (http://www.innovation.gov.au/page/innovation-connections). In Canada, funding of clinical trials on natural health products through federal agricultural institutions including Agriculture and Agri-food Canada has been possible of late and is particularly visionary. Their concept is that the demand for a crop or food is dependent to a large extent on the public's belief that ingestion of that food will have health-related benefits (Fig. 1). A health benefit due to ingestion of a crop or food will lead to increased demand for that crop or food. Increased demand for a crop will in turn ultimately produce higher prices for that crop and larger acreage devoted to the crop. Both will stimulate the agricultural industry for that commodity right from the farm gate to the marketplace (Qaim, 2016). The impressive rise in the cultivation of canola from 6.25 million acres in 1990 to 20.6 million acres in 2015 in Canada (http://www.canolacouncil.org/markets-stats/statistics/harvest-acreage/) with increased use of canola due to its positive health benefits is an excellent example of this. The income to