Food Health Claims – Physical Performance

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INTRODUCTION

Physical activity, athletic performance, and recovery following exercise can all be enhanced by optimal nutrition, using an appropriate selection of foods, fluids and supplement choices for optimal health and exercise performance. This provides an excellent opportunity for innovative sports nutrition companies to develop functional products aimed at enhancing physical performance in a range of target populations, from the elite athlete to the elderly who are at risk of sarcopenia (degeneration of skeletal muscle mass and quality).

Once the goals have been established, it's time to select a clinical trials provider and design the study.

HOW TO SET ABOUT DESIGNING A CLINICAL TRIAL

To design the optimal clinical study, it is always best to start with the end goal in mind. This means you should start by specifically determining the following goals: 1) scientific, 2) regulatory, and 3) marketing.

1) The scientific goals of a clinical study (endpoints) can include determination and demonstration of efficacy and safety, as well as understanding and validating the mechanism of action. It is important to understand the population for whom the product will work best, and design the study around this target population. For foods and supplements this should be a generally healthy population, including those at risk of disease. For physical performance trials this can include subjects exposed to a high mechanical load through sports activities, manual labour or obesity, and people with joint or muscle deterioration due to normal ageing. In reviewing the rejected documents, it is clear that EFSA considers studies performed on non-healthy, diseased subjects as not applicable to health claims for healthy consumers of supplements and functional foodstuffs.
2) The regulatory goals of a clinical study should include establishing clinical proof of a beneficial physiological effect for your functional ingredient or product, and determining that the substantiation for your product specifically stems from an active ingredient within your formulation. For studies that may be submitted as part of a dossier to EFSA, the food/constituent must be sufficiently characterised, and it is crucial that a cause and effect relationship is established between consumption of the active ingredient and the study endpoint. In the USA, the FDA draft guidance published in October 2010, titled "Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted without an IND" specifically exempts dietary supplement clinical trials from IND

requirements, as long as the dietary supplement is being used to affect the structure and/or function of the body.

3) Design the trial to suit the marketing claim. When designing a clinical study the consumer (marketing) benefits should also be borne in mind, specifically for wording for any on-pack health claims that the company may seek from regulatory authorities, such as EFSA. Other marketing benefits would include press-worthy events (peer-reviewed publications and/or scientific poster presentations).

WHAT EXPERTISE IS NEEDED TO CONDUCT A STUDY?

According to the EFSA guidance document on scientific requirements for health claims related to physical performance (EFSA J, 2012, 10 (7), 2817), "physical performance relates to the ability to complete certain physical tasks with higher intensity, faster or with a higher power output". There is a wide range of different areas that fall under into this category, such as individuals performing exercise for sporting endeavours (e.g. elite athletes), as part of their work routine (e.g. construction workers) or for recreation purposes (e.g. recreational athletes), but also assessment of physical performance in an elderly population who are going through the natural ageing process, resulting in muscle and/or joint deterioration. The type of exercise in athletes can range from acute, high-intensity activity (e.g. sprinting) to longer term endurance activity (e.g. ironman triathlons), weight bearing (e.g. running) versus non-weight bearing (e.g. swimming), and in a more sedentary population will range from measures of mobility to muscle function.

There are a number of options for companies looking to carry out a clinical study to assess the efficacy of a functional ingredient that may improve physical performance. Typically studies like these are either carried out through academic research laboratories, with a specific expertise in clinical research, or through clinical trial companies which are specialized in carrying out trials with food ingredients or supplements (rather than pharmaceutical drugs). Below is a check list of the types of expertise that companies should look for when choosing a clinical study provider.

1. Clinical/sports medicine expertise for study design

In order to design the optimal clinical study to look at physical performance, it may be necessary to involve medical and sports training experts with backgrounds in areas such as sports medicine, rheumatology, orthopaedics, qualified sports trainers and physiotherapists. These clinicians and trainers will help design the intervention study by drawing on their previous experience of inclusion and exclusion criteria for subject selection, how often and when to dose, optimal dosage, selection of primary and secondary endpoints and assessment methodologies. Together with the clinical team (see below) they will recommend the type of study that is best suited, such as a parallel versus a cross-over design. In many geographical areas, in order to obtain ethical permission to carry out the proposed clinical study, the Ethical Review Board will often require that the Principal Investigator on the clinical study is medically qualified.

2. Access to world-class sports facilities

Any study involving physical performance will most likely include some aspect of a physical training programme. In clinical trials we have carried out, these training regimes can range from studies requiring that the participants undergo four weekly resistance training programmes (e.g. the use of equipment and weights to work on specific muscle groups, alternately concentrating on upper versus lower body) for studies looking at assessing muscle strength, to sarcopaenia studies in the elderly, which benefit from a functionally-oriented exercise training programme to help build up overall fitness, mobility and strength.
Access to world-class training equipment and specialised certified trainers is essential to carry out a validated study. The types of equipment need will vary from resistance equipment and free weights for strength/muscle mass studies, to treadmills, steppers, cross trainers, bikes and rowers to provide aerobic workouts. An indoor running track will allow measurements such as sprint times (athletes), or 6 minute walk test (elderly) in a controlled environment that is not subject to weather conditions (such as wind, heat, rain). Use of computerized equipment will permit tracking of the subjects training compliance and performance. Systems to assess periodically the study endpoints (such as 1RM – see below), and different certified trainers who are not involved in the training regime, will also be necessary to ensure bias is not introduced into the study.

3. Clinical team with expertise in carrying out studies

A critical requirement of research involving human participants is the adherence to the principles of good clinical practice (GCP), including adequate human subject protection (HSP). Hence it is essential to ensure that the organisation that conducts your study carries out trials to GCP standards, has suitable standard operating procedures (such as safety procedures) and an external monitoring regime. It is also important that the study team understands the intended claim that the sponsor company would like to achieve and the regulatory requirements.

The clinical research team involved in physical performance trials will typically include a principal investigator (discussed above), a clinical trials co-ordinator/project manager (will oversee the study, including ethical submission, quality, subject recruitment), clinical nurse manager, nutritionist (will evaluate the diet of the subjects to ensure they continue to meet eligibility criteria), statistician (will statistically power the study, develop the statistical analysis plan and carry out statistical analysis), certified trainers to monitor the regular training sessions (from a performance and compliance perspective), certified trainers/assessors who carry out the assessments for the clinical endpoints. An external monitor will also be needed (can be provided by the sponsor or the clinical trials organization) to ensure studies are carried out to GCP standards.

When designing clinical intervention studies with food ingredients, the nutritional background of the subjects and the control group needs to be taken into consideration. This is to ensure that the subject is not already ingesting large amounts of the test ingredient in their diet, or if the ingredient is a compound that is ingested regularly (e.g. caffeine) that the control group is taking consuming similar amounts in their background diet. For sports studies, particularly those looking at building muscle, it is often important to know the calorie intake of the subjects. You should also ascertain the clinical trial

providers' ability to provide standardized meals, as these will often be necessary for the subject visits when assessments are being carried out. Hence the clinical team will need a nutritionist.

4. Access to the relevant population and recruitment expertise

The population in which the clinical study is carried out should be a generally healthy population, and should also be representative of the target population for the final product. Hence this can vary from elite athletes, to recreational athletes to the elderly. Depending on the target group of the consumer product, the study site should also have access to subjects with different types of sports backgrounds e.g. resistance training versus cardiovascular training, male versus female. It will be important to establish if the clinical study provider has a database of volunteers, recruitment officers and their ability to advertise. If it is a large study, does the clinical provider have multi-site capabilities?

5. Ensuring compliance

It is important in any clinical study to ensure that the subjects are compliant on a number of levels. Firstly with consuming the test product both at the dose level and times required, so the clinical site will need systems in place to monitor this. This can include random spot checks, blood sampling, consumption of study product at the clinical site etc. It will also be important in physical performance trials that the subjects are compliant with any training regimen, which is very often part of the clinical protocol. For studies in which there are compulsory resistance training sessions this can be achieved through supervised training sessions and the use of resistance training equipment with computerized log-in system that tracks the performance of subjects. In other studies where a certain level of physical activity may be required (e.g. sarcopaenia studies) regular assessment of training activity through the use of questionnaires (e.g. IPAC International Physical Activity Questionnaire) will be necessary. It is also important that the site is familiar with dealing with missing data when subjects drop out.

6. Measurement assays suited to food interventions

Another critical element to any intervention study will be the assessment of the clinical endpoints chosen for the study. For sports performance studies, there will often be a combination of physical endpoints e.g. muscle strength, agility, endurance, and body composition, used in conjunction with other outcomes such as changes in biomarkers.

6.1 Physical endpoints

For sports performance studies there can be a variety of different measurements, depending on the study design, that will measure physical aspects such as muscle strength, body composition (to ascertain if there has been an increase in muscle), endurance and agility. Some examples of the different types of assessments suitable for physical performance clinical studies are below -

-Strength and agility assessments - one repetition maximum weight lifted (1RM) is the most widely used measure of muscle strength; the Biodex system is a piece of equipment which can measure isokinetic function (eccentric and concentric) and isometric strength, on all the major muscle groups;
-Endurance and cardiorespiratory fitness - endurance capacity using lactate threshold, multi-sprint endurance; O_2 uptake, CO_2 production, maximal aerobic capacity (VO_2max), anaerobic threshold, lung function e.g. PEF (peak expiratory flow), vital capacity, % FEV (forced expiratory volume)
-Physical performance - reduced time taken to run/cycle a certain distance, increased acceleration, 1RM, jumping height, aerobic capacity/VO_2max, economy of motion, muscle fatigue, flexibility and range of motion, abdominal strength.
-Body composition measurements e.g. % lean muscle, body fat, etc. using either DXA or bioimpedance, anthropometric measures such as muscle circumference.
-Fat & carbohydrate metabolism - indirect calorimetry (e.g. Cosmed Cardio Pulmonary Exercise Testing CPET) enables the assessment of fat & carbohydrate metabolism, energy cost of exercise, resting metabolic rate, inspiratory and expiratory lung function.

To assess physical performance in the older adult, a series of functional tests suitable for this cohort will be required, such as
-Handgrip strength or quadriceps strength (e.g. 1RM)
-6 min walk test (ideally on an indoor track), timed get up and go, chair stand, stair climb power test
-Agility, gait speed, flexibility

6.2 Biomarkers

Other endpoints often used are biomarkers, and as clinical studies with food ingredients will usually result in a smaller effect (than a drug) in a healthy population, the assays that are used will often need to be more sensitive to detect changes in biomarkers (e.g. small changes in inflammatory biomarkers such as C-reactive protein, or CRP). The US National Institute of Health define biomarker as ”a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or responses to a therapeutic interventions”. So it is important that the clinical provider can carry out sample analysis that is sufficiently sensitive. Occasionally, in order to ascertain mechanism of action for products that act to build muscle, a sponsor may wish to establish if there has been uptake of the active ingredient into muscle tissue, or if there has been a change in some aspect of muscle structure (e.g. increase in mitochondria), which would typically be ascertained through a muscle biopsy. Ethical approval for this invasive technique in most jurisdictions will be a challenge and most Ethics Boards will require prior proof that a muscle biopsy will provide this information (e.g. prior data from animal models) in order to judge the potential benefit of such clinical data to the intervention study versus the subject safety.

CONCLUSIONS

Consumer awareness of the importance of nutrition, and the impact of functional food products on potential lifestyle and health benefits is continuing to grow. Clinical trials are now an essential

component of any R&D programme for foods and food constituents, in order to increase support for health claims. Many factors must be considered in the design of clinical studies for physical performance to ensure that the objectives of the study will be met and to ensure that the results collected will be relevant to the proposed health claim.

Other aspects to consider when choosing a study site will be confidentiality, timing of the study (both when the study would start, proposed study recruitment duration and overall study duration), invoicing process, registration of the trial on a clinical trials register (e.g. clinicaltrisl.gov), a publication in a peer-reviewed journal, oral presentation at conferences.

In conclusion, it is essential to select a clinical trial provider carefully, weighing up the aspects covered in this review, in order to choose the site best suited to deliver a carefully designed study on time and on budget.