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Prove it!

The power of clinical trials

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Investing in research and substantiation boosts market and consumer confidence

by Charlotte Bastiaanse

Newsflash: The days of churning out nutrition and health products to market with no accounting for safety and efficacy are long over. In an already highly competitive and saturated industry that revolves around changing consumer behaviour, businesses are doing everything they can to meet demand and offer differentiation.

In recent years, the need for validated health claims in the form of substantiated science has become somewhat unnegotiable, leading to a considerable increase in the number of businesses investing in clinical trials. More nutraceutical, food and beverage manufacturers involved in the development and commercialisation of their respective products are joining the industry-wide trend through collaboration with research partners that can support clinical investigation and file preparation.

Researchers have long explored the science of nutrition and food-related health benefits through various pathways; however, randomised, double-blind, placebo-controlled trials have emerged as the gold standard of clinical evidence for drugs, nutraceuticals and functional foods.

In this report, we investigate how clinical trials have been repositioned, implemented and utilised across the industry. Together with five market experts, we delve into why trials are needed, the investment required from businesses, and the potential challenges that may be experienced along the way.

Scientific substantiation

As with all trends and movements within the nutraceutical industry, empowered consumers who pay attention to what they put in their bodies are insisting on validated research that supports finished product health claims.

"In a digital age, people are far less dependent on their doctors for advice, and are increasingly able and willing to take greater control of their own health," says Jayesh Chaudhary, founder and CEO at Vedic Lifesciences.

"Consumers are confident in their ability to take responsibility for their health and know how to access online resources to help them do so."

According to a study released by the Pew Internet & American Life Project, researchers found that 80% of American Internet users have searched for a health-related topic online; however, just 12% believe nutrition researchers are transparent about potential conflicts of interest with industry. Additionally, Americans have more positive and trusting views of dietitians (54%) than nutrition researchers (28%).

Ecommerce has undoubtably put the power in consumers' hands, and health-conscious shoppers invest the time in researching, validating and purchasing the vast array of products available through online retail. Scientific substantiation in the form of a clinical trial truly can make the difference when it comes to swaying consumer purchasing decision. According to Mariko Hill, product development executive at Gencor, consumers understand that "not all supplements are created equal" and that efficacy can differ for the same ingredients when it comes to bioavailability and functionality.

Rosario Russo, scientific officer at Giellepi SpA, adds that in addition to scientific evidence around efficacy, consumers are also concerned about safety—especially surrounding dietary supplements and functional foods and beverages intended for long-term consumption.

That emphasis on safety is being driven by other quarters as well, according to Barry Skillington, chief commercial officer at Atlantia Food Clinical Trials. He comments: "Demand is further driven by regulatory bodies' requirement for scientific substantiation which invariably takes the form of a human clinical trial. Randomised human clinical trials are considered the gold standard of evidence for the scientific substantiation of claims by the European Food Safety Authority (EFSA), the U.S. Food and Drug Administration (FDA) and other regulators around the globe. Randomised controlled trials (RCTs) add the depth of knowledge required by consumers to make informed purchasing decisions which will not negatively impact their wellbeing, whilst providing effective product ranges for disease prevention."

Consumers may be driving the demand for clinically validated research to support health claims, but this does not necessarily mean they fully understand the data behind such claims. This is where brands can look to healthcare professionals, dietitians and even influencers to fill in missing

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education portions, simplify the data and ultimately drive positive impact on consumer purchases.

Clinical trials plugging holes

The food and beverage and nutraceutical sectors have faced multiple challenges in recent years, particularly in terms of regulations around the marketing of functional foods and their associated health claims. Nutraceutical and food companies have realised products that don't have a clinically validated health claim can't deliver on consumer confidence. Clinical studies are an investment that continue to reap benefits rather than a cost, says Chaudhary.

Skillington adds that boundaries between some drugs and functional foods are blurring as the two sectors look to meet the needs of the same consumers, but with different purchasing approaches.

Many pharma companies have developed an interest in the nutraceutical market, driven especially by consumers looking to complement health through food. However, Russo comments, "in what has grown to be a large market, the need to distinguish is raised—confirming the quality of products through science resembles more of a pharmaceutical approach."

Hill adds that by manufacturing to pharmaceutical standards, ingredients will be manufactured at the highest quality and validations, ensuring full safety and efficacy profiles.

According to Skillington, Good Clinical Practice (GCP) is the same for food and drug trials with many of the detailed procedures and processes overlapping. He notes that foods have a lower effect size generally, but a broader buying audience, while drugs have a higher effect with a narrow consumer focus. That said, food companies have upped their game considerably over the past decade as it relates to the research and development process.

Supply chain and branded finished products

When looking at the B2B supply chain, a majority of clinical trials are taking place at the ingredient level to validate associated health claims. The availability of clinical data is becoming a strong negotiation tool, especially in B2B scenarios, says Skillington. Suppliers that can support validated health benefits will have a competitive advantage, as many researched ingredients are sold at premium prices.

Validated ingredients are then sourced by brands looking to retail finished products that can legally carry the desired claim on pack. However, finished products are rarely tested in human studies, especially those that incorporate a final formulation that blends various ingredients which may deliver different, or even opposite, effects. The need for finished product trials will differ from product to product and from market to market.

Combinations in formulation have the potential to either improve or diminish the effect of the finished product, which opens up new questions surrounding the recommended dosage levels that support the efficacy and safety of the product that ends up on the retail shelf.

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"Preclinical studies can be useful in supporting the explanation of a particular combination of ingredients in a dietary supplement and pharmacokinetics studies can support the superiority of a specific product compared to competitors," says Russo.

The grey area of expanding to test finished products ties back to consumer trust. Trialling the performance and efficacy of a combination-type finished product will lend further insights surrounding the product's ultimate success. When a consumer buys into a long-term-use product, they hope to see or feel a difference that validates the investment. Scientific testing that supports manufacturer and buyer confidence go hand-in-hand in securing brand loyalty, shopper satisfaction and long-term commitment.

Investment at all angles

Although nutraceutical and functional food companies understand the importance and value of clinical trials, it's a costly exercise that involves time, resource and monetary hurdles. Additionally, there are costs associated with other influential factors, like recruiting trained personnel to develop study design, analysing the results, and interpreting data for product development. Businesses need to keep the depth of investment required across all areas front of mind before embarking on a trial; to put some numbers in perspective, Skillington shares that the total value of trial costs depend on a number of factors, specifically the number of participants. Food trials can cost between €3,000 and €10,000 per person. There are also fixed costs to consider, starting at €50,000, as several aspects of the trial are not variable. "Trials might start from €100,000 but this would be one with a small pool of participants, few visits and minimal trial procedures. The average randomised controlled trial designed with enough statistical power to show significant differences between groups are set around €250,000. Trials costing €150,000 are possible, but they tend to be pilot or not placebo controlled in nature." These figures are merely benchmarks for commercial third party partner trials and will differ from study to study.

Russo adds that even if the market is moving in clinical trial direction, not all companies, especially medium and small firms, are able to keep up with the trend nor do they have readily available funds to make such large investments. "It takes time to understand how and how long it will take for clinical trials to change the market. Moreover, often the monetary investments are not proportionate considering the turnover of nutraceuticals compared to drugs."

While trials can be a costly hit for smaller companies, they can provide quick competitive advantage over other companies of similar size, yielding faster immediate return on investment.

Market experts agree that companies can get clever with cutting their costs as multiple factors—partner, sample size, population group and the science needed to measure final outcomes—contribute to the overall investment of clinical trials.

"Certain countries, like India, can provide a cost advantage with the same level of expertise," says Chaudhary. Clinical trials companies will also be able to recommend and execute different approaches depending on the company's financial capacity.

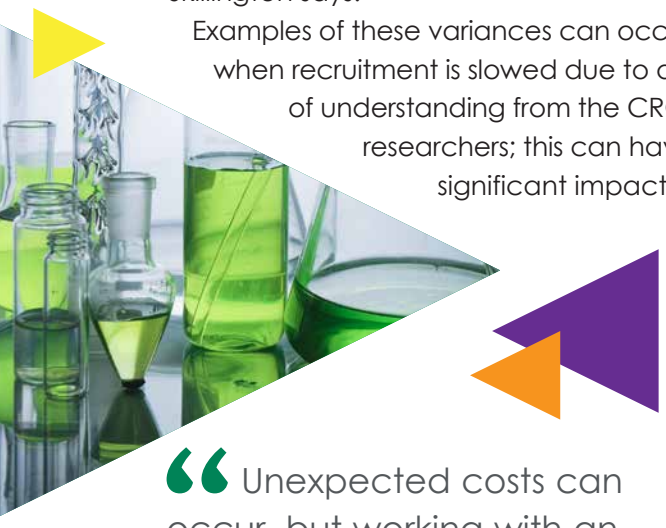
Russo suggests that if companies are struggling to find investment, perhaps gaining practical insights through case studies with research teams, or even looking at smaller-scale pilot trials.

When it comes to the current climate across the industry, the proliferation of clinical data is making it challenging for companies to compete if they lack evidence pertaining to the effects of their products in humans, says Skillington. "Clinical trial data can enable companies to capture market share and command premium prices, but companies—big and small—must inevitably invest time and money to generate the evidence that unlocks these opportunities."

The time needed to conduct a clinical trial is one thing; the time needed for planning and analysis is another. Ultimately, the development process that leads to a final product launch will depend on these timelines.

"Timelines and budget will vary depending on many attributes such as the type of partner the organisation is working with, the sample size required to show effect, the difficulty level in population selection, and the scientific knowledge and technology needed to measure the desired outcomes," Skillington says.

Examples of these variances can occur when recruitment is slowed due to a lack of understanding from the CRO or researchers; this can have a significant impact on the trial budget and timeline. Skillington further explains, "The second most interruptive factor on budget and time is the lack of availability of the test product or placebo. Too many times sponsors leave this detail too late and when the test material is delayed, the entire trial process is thrown out, costing money in terms of team compensation and time lost."



Unexpected costs can occur, but working with an experienced research partner on a carefully planned project should ensure that timelines and budget modifications are reduced as much as possible.

Working with CROs

So, who do businesses turn to when the time comes to put together a clinical trial? CROs and universities are commonly selected as research partners, but there are complex layers that businesses need to consider in their selection process.

While a good amount of clinical research is being done in the university setting, many nutraceutical and food companies have turned to CROs to deliver the research and business benefits they're seeking.

"It's worth noting that many university human trials units will work to, or are working towards, ICH-GCP standards," says Iain Brownlee, associate professor of nutrition at Northumbria University. He adds that one key element for companies in deciding who to work with for a trial on their product will be the level of relevant capability. The level of expertise at running food- or nutraceutical-based clinical trials and the necessary facilities specific to the study (relevant storage and food preparation facilities, live-in rooms and outcome measurement testing) has to be available at the facility of choice.

Partner selection is a process which requires trust on both sides of the agreement. Skillington explains, "It's equally critical that

the CRO is on board with the project and believes in the science behind the product in order for them to represent and do justice by the study. Reputation is at stake on each side of the equation."

As a starting note, RCTs must use suitable outcomes, study populations, controls and actions to reduce bias. Decisions made early in clinical development are critical. Large food and supplement companies are hiring clinical program managers, regulatory professionals and people with experience running trials in the nutraceutical industry in order to ensure that their clinical programs are run to suitable standards. "Outsourcing clinical development to a service provider frees companies from the need to establish in-house capacity outside of their core competencies and greatly reduces bias in terms of the effect noted in the studies," Skillington says. "Faced with these pressures, small and large companies alike have turned to full-service CROs, however, this approach will only pay off if a suitable service provider is selected."

Officially, studies must comply with GCPs set by the International Conference on Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCPs).

In recent years, organisations like EFSA and FDA have improved efforts to make clinical trial populations more representative. This can be achieved thanks to multi-centre trials. Skillington notes that while single-centre studies maximise control, multi-centre trials offer access to more diverse populations that better reflect the consumer population as a whole.

One way to resolve this challenge is to use multiple study sites that are all owned and operated by a single CRO or a group of CROs, rather than activate third-party hospitals and medical centres. This approach to multi-centre randomised clinical trials provides enough sites to capture a diverse subject population without relinquishing control to centres that may compromise ICH-GCP compliance.

There is still a discrepancy between quantity and quality. Although randomised double-blind, placebo-controlled trials have become the standard, there are still plenty of questionable factors that require investigation beyond the abstract. As an example, Chaudhary considers the university versus CRO scenario of a clinical trial conducted by a sponsor together with a research partner. "The quality of the data is likely to be superior with a CRO. This is because statistically-relevant numbers can be difficult to achieve and inclusion criteria is often compromised due to absence of a third party auditor in a university. The CRO is able to provide unbiased results and, thus, more credible claims."

The best CROs know how to design trials, look at statistics and analyse data in a manner that gives their studies every chance of succeeding, whilst providing an end-to-end service.

Brownlee comments, "As randomised, controlled trials have become synonymous with health claims, many companies may be tempted to jump straight to that form of evidence development. In my view, this could limit the potential for positive outcomes." Working with a partner who can provide a range of methodologies outside of participant-based trials may be beneficial in the long-run. Laboratory-based testing or systematic reviews can help inform study design better, develop more targeted outcomes (and so reduce study cost) and even highlight where randomised, controlled trials are not feasible or justified. "All scientific

studies are expensive and companies should approach new products with potential health claims with long-term research strategies and trajectories. Believe in your own products, but not enough to forget to question your original assumptions," adds Brownlee.

Shifting timelines

Once a business has determined its research partner, the final design and implementation phases can move forward. When obtaining clinical data, control and compliance to certain standards (ICH-GCP) is highly important.

"At Atlantia Food Clinical Trials, we consider the end-to-end process as: study design, protocol development, ethics approvals, subject recruitment, study conduction, quality and data management, sample analysis, biostatistics, dietary analysis and reporting," shares Skillington.

The time needed to design, conduct and publish a clinical trial is anywhere between eight and 18 months. The design, recruitment and conduction phases take roughly three months each.

However, there are numerous factors that can influence the final timeframe, such as number of participants, types of participants, type of study—pilot trial, pharmacokinetic study, cross-over—length of study, and additional number of markers.

"Additionally, start-up procedures for preparing all documents for ethical committee approval require time," Russo says. "In particular, ethical committee approval, which usually varies according to the country, may significantly affect timelines."

Timelines can also shift depending on the location of the research partner and its ability to recruit at a fast rate.

"Drop-outs, delays in delivering product, faults in product quality (placebo and active ingredients), and participant incentives are example factors that can lead to unexpected costs," adds Hill.

Results upon completion

Final data interpretation, which could be seen as peripheral, has a huge effect on the outcomes of clinical trials. Interpretation can be conducted by the sponsor, the research partner, or both—all depending on their individual and joint capabilities.

All companies set out hoping to receive results that meet their investment and scientific goals in order to justify certain health claims and ultimately make their product commercially viable, Hill says.

When looking at the results, the principal investigator usually has an input as well as the medical team and statistics teams at the CRO. Companies might want to publish their results or even pursue a health claim, nevertheless, certain standards need to be met to achieve either. "Even more strict requirements are needed when obtaining a health claim, such as duration of the intervention, primary outcome design, number of subjects, reproducible cause and effect among others. A dossier will contain data from several clinical studies and will usually contain a pilot study and/or a dose ranging study as well as the pivotal research," explains Skillington. Being aware of those requirements is fundamental for those companies aiming to accomplish such goals.

Regarding the publication of such data, Russo adds that companies can involve academic key opinion leaders, skilled on the topic of the clinical investigation, asking for their collaboration and support for writing the manuscript and submission to scientific peer-reviewed journals. ●

Biographies

Dr Iain Brownlee, associate professor of nutrition, Northumbria University.

The scope of his previous research is broad but has included supporting large and small companies in consideration of development of potential health claims and designing, running and managing randomised, controlled trials and other participant-based studies. He has collaborated with experts from food, pharmaceutical and biotechnology industries throughout his career. His work has resulted in three patents and over 40 peer-reviewed publications. He is also involved in ongoing international collaborations in Singapore, Malaysia, Australia and the Republic of Ireland.

Jayesh Chaudhary, founder and CEO, Vedic Lifesciences

Over the last two decades, Chaudhary has been a thought leader and innovator in human studies on dietary supplements. He has been active in the food supplement industry since 1994, and is one of the pioneers introducing good clinical practices (GCP) and other stringent standards to natural product research. Chaudhary has written for industry publications, co-authored several original papers and reviews, and is a strong advocate for fast-tracking innovation in the nutraceutical industry.

Barry Skillington, chief commercial officer, Atlantia Food Clinical Trials.

Skillington has over 25 years' experience working in the commercial food sector in both product development and business development, in both Ireland and in the United States. Having spent the last seven years at Atlantia as CCO, he has helped build the brand and customer base to where it is today as one of Europe's leading food clinical trials companies. Atlantia is a full-service CRO, specialised in delivering ICH-GCP standard clinical studies. The company owns its own clinics, in Ireland and the United States, where they conduct acute, observational and intervention studies for functional foods and beverages, nutraceuticals, prebiotics and probiotics, medical foods, dietary supplements, infant formula and microbiome-based therapeutics.

Mariko Hill, product development executive, Gencor

Hill, based in California, is an international athlete with a particular interest in the impact of nutrition on performance and recovery. Utilising her knowledge in the field of exercise and nutrition and further experience as a research fellow from the University of Oxford, Hill is responsible for new product development and business development at Gencor.

Rosario Russo, Ph.D., scientific officer, Giellepi SpA

Dr Russo received his doctorate in toxicology in 2010, focusing his research on preclinical evaluation of biological activity of natural products. He was trained in pathology and technologies applied to laboratory animals and in 2013, received his master's in preclinical and clinical research and development of drugs. From 2006 to 2013, he worked at University of Naples Federico II (Italy) in the toxicology laboratory, during which time he collaborated with many public research organisations. He is author of many original manuscripts which are published in indexed international scientific journals.

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CONTACTS

As the official media for Vitafoods Europe and Asia, Vitafoods Insights explores emerging areas and key issues across the global health and nutrition industry, helping business executives make informed, strategic decisions. Vitafoods Insights reaches a broad audience of professionals, and shares the passion of enriching industry knowledge and growing the health and nutrition market.

Jon Benninger
Vice President & Market Leader, SupplySide Portfolio
jon.benninger@informa.com

Heather Granato
Vice President, Content
heather.granato@informa.com

Danielle Dunlap
Vice President, Marketing Services
danielle.dunlap@informa.com

Madison Dorn
Program Coordinator

Andrew Rosseau
Art Director

Informa Markets
2020 N. Central Ave., Suite 400
Phoenix, AZ 85004
United States

Phone: +1 480 990 1101
www.naturalproductsinsider.com

Chris Lee
Managing Director, GHNN Europe
chris.lee@informa.com

Gareth Morris
Head of Sales
gareth.morris@informa.com

Maria Sidiropoulou
Sales Excellence Manager
maria.sidiropoulou@informa.com

Daniela Elia
Head of Marketing
daniela.elia@informa.com

Stephanie Campos
Client Success Executive
stephanie.campos@informa.com

Charlotte Bastiaanse
Associate Editor
charlotte.bastiaanse@informa.com

Informa Markets
240 Blackfriars Road
London SE1 8BU
United Kingdom

Phone: +44 (0) 20 7921 5000
www.vitafoods.eu.com

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