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National Institute for Health Research

Cancer and Nutrition NIHR infrastructure collaboration

Steering Committee Document Tracking Form

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Document	**Background Document to developing the Commercial/Industry Engagement Strategy**
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Version	**0.4**
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Comments	**This is a new version of the document, a previous version was presented to the Steering Committee in June 2016. The purpose of the new version is to capture all the relevant elements of working with the commercial sector, and to set out some short, medium and long term aims.**
Action	**For discussion and agreement of next steps**

Cancer & Nutrition NIHR infrastructure collaboration – Background Document to developing the Commercial/Industry Engagement Strategy

1. Introduction

This document will set out the background to developing the strategy for the Cancer & Nutrition NIHR infrastructure collaboration to engage with industry.

Background to the Collaboration

The prevalence of cancers is increasing worldwide and in the UK, and this is particularly true for the burden of preventable cancers related to nutrition. Nutritional factors are increasingly recognised as a growing cause of morbidity and mortality, including from cancers, and there are substantial research efforts directed to a better understanding of how cancer might both be prevented, and treated, and the lifestyle factors which contribute to cancer development. The disciplines of cancer and nutrition each draw on a wide range of science, skills, and expertise but are not well coordinated and the sharing of knowledge, information and expertise between them is poor.

The UK has world class research both in nutrition and in cancer, but there has historically been little joint research in these areas. It has become apparent that the discrete area of nutrition and cancer represents an untapped field of scientific endeavour. The Cancer and Nutrition NIHR infrastructure collaboration was established in 2014 to bring coherence to existing activities and provide a coordinated framework for future research in the areas of cancer and nutrition.

Vision of the Collaboration

Our vision is to establish a coherent and effective infrastructure to enable the best quality translational research agenda which will bring nutritional considerations into all aspects of cancer prevention, treatment and care, and to establish mechanisms through which every person and health professional can know and understand how best they can contribute.

Aims of the Collaboration

Our long-term aim is to improve the nutritional care and advice that patients receive by bringing coherence to existing activities in nutrition and cancer. This includes the following objectives:

- To create a framework as a basis for future research into cancer and nutrition
- To establish better networks for sharing knowledge between stakeholders.

2. Working with Industry

There is an explicit recognition of the need and value of developing partnerships between patients, researchers and the commercial sector and industry to accelerate and enable nutrition translational research. Multiple sectors across the food and nutrition industry, as well as the life sciences industry, wish to engage in

translational research. They would benefit from a direct and simplified route to the range of experimental medicine facilities and expert investigators and clinicians. The collaboration actively seeks to engage with such partners to bring new diagnostic tests and treatments to patients faster. The NIHR Office for Clinical Research Infrastructure (NOCRI) provides potential partners with a means of working together with the collaboration. The life sciences industry, especially the pharmaceutical industry, have established and secure terms of engagement and governance processes that oversee research activity. These terms and processes are less well established for all aspects of the food and nutrition industry and commercial sector. The purpose of this document is to offer the background and framework that needs to be taken into consideration in developing the collaboration's strategy for developing partnerships with industry and the commercial sector.

Scope of Research

Nutritional science and the role of nutritional care in enhancing patient outcomes continues to evolve. The collaboration actively seeks to engage with industry as it relates to cancer and nutrition. This engagement embraces a wide range of different sectors that include:

- food and food products (growers, producers, retailers, distributors, catering industry, trade associations and confederations),
- dietary supplements – amino acid, vitamin and mineral supplements, fish oils, etc
- probiotics (including live faecal matter transplants or microbiome)
- 'functional foods' and 'nutraceuticals',
- foods for special medical purposes and clinical nutrition support,
- devices for assessing nutritional state – body composition, functional capacity (eg grip strength), laboratory analysis (eg biochemistry, mass spectrometry), movement accelerometers, heart rate monitors, indirect calorimetry,
- electronic/web technology – apps, online coaching/eHealth
- health insurance companies and other industries interested in promoting healthy living

Each sector offers different opportunities for investigator-led collaborative research with a focus on early clinical studies (Phase I/II) within Biomedical Research Centres through to studies of effectiveness and implementation across other aspects of the NIHR infrastructure. This research needs to be conducted within a clear and transparent governance framework that adheres to ICH GCP guidelines and other regulatory instruments (eg MHRA, ABPI, etc).

The food and nutrition industry that has emerged over the last 50 years has moved beyond the production and provision of foods in their natural state as basic food ingredients or conventional foods as grown and marketed to provide nourishment. The development of manufactured and processed food products now embraces considerations of dietary supplements, functional foods, nutraceuticals, medical foods (foods for special medical purposes and clinical feeds administered orally or by artificial means through tube or vein). The lack of definition of many of these terms, the evolving regulatory framework around health claims and uncertainty whether a product should be considered as a 'medicinal product' or a "food" poses a challenge for both investigators and industry, and the regulators. A working definition is given in Appendix 1.

Regulatory framework as it relates to food and nutrition

To protect public health, and on behalf of the UK Licensing Authority, The Medicines and Healthcrae products regulatory Agency (MHRA) regulates medicinal products for human use in accordance with the European Community's medicinal European Community's medicinal products directive (Directive

2001/83/EC, as amended, “the Directive”) and UK law. The MHRA may be asked to give an opinion on, or make a formal determination on whether a product is or is not a medicinal product. The regulatory status of products on the borderline between medicinal products and food supplements may not be immediately obvious (MHRA Guidance Note 8 - A guide to what is a medicinal product. March 2016)

The extent to which a nutritional product presents a health claim or purported benefit to either prevent or modify disease, means that some food products or bioactive compounds that originate within food are purposively seeking effects more usually associated with drugs (pharmacological effect), yet still may be considered as foods. This confusion is one of the reasons for the difficulty in agreeing the regulatory and governance frameworks around both research and the marketing of such products. One of the immediate concerns for research is whether trials that examine the effects of food products, functional foods, or nutraceuticals on the prevention or treatment of disease should be seen as or considered clinical trials of a medicinal product (CTIMP).

The MHRA determines whether a product falls within the definition of a medicine (‘medicinal product’) or a medical device and provides information on whether or not a product is a medicine or a medical device. MHRA decides whether the claims that are made or the active substance(s) present would mean that the product should be regarded as a medicinal product.

A medicinal product is:

- *any substance or combination of substances presented as having properties of preventing or treating disease in human beings (the first limb)*
- *any substance or combination of substances that may be used by or administered to human beings with a view to restoring, correcting or modifying a physiological function by exerting a pharmacological, immunological or metabolic action, or making a medical diagnosis (the second/functional limb).*

Products can fall within the definition of a medicinal product if: (a) they make medicinal claims; (b) if they modify physiological functions by acting pharmacologically, immunologically or metabolically.

Many nutrition products fall within a grey area where they may be seen as foodstuffs and so need to comply with food safety and labelling legislation rather than considered as medical products. For example, the MHRA do not consider food supplements that contain familiar substances like vitamins, amino acids or minerals consumed at levels comparable to dietary intakes as medicinal products and these are generally subject to food safety and food labelling legislation rather than medicines control. However, there is increasing concern that the nutraceutical approach may be moving beyond what could be considered familiar (eg never consumed as part of a normal diet or consumed at intakes far greater than can be achieved within the diet) and are intended to act pharmacologically, immunologically or metabolically to modify a disease process or be used as part of a therapeutic intervention. In these cases it will be the claims being made and the mode of action that will decide which regulatory regimen will apply.

In the EU, foods for special medical purposes (FSMP) are a sub-category of foods intended for particular nutritional uses (PARNUT), also called “dietetic foods.” PARNUT has now been replaced with the Foods for Specific Groups Regulation to ensure a consistent approach across Europe. FSMPs use specially processed or formulated nutritional products intended for the dietary management of patients and to be used under medical supervision. They are intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary foodstuffs or

certain nutrients contained therein or metabolites, or for those with other medically determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone, by other foods for particular nutritional uses, or by a combination of the two. FSMPs are the most medically-oriented food category (all other food products, including supplements, are forbidden from even mentioning the word "patient" or "disease" on their labels). Indeed, FSMPs are attractive for manufacturers, since it is possible to make strong claims while avoiding the restrictions of the Health Claims Regulation. The wording of the respective claim is mandated by the relevant regulation and goes along the lines of "for the dietary management of [a certain illness]." In order to be marketed as an FSMP, the food must meet a number of criteria. First of all, the food must be safe and must comply with the intended purpose and requirements of the regulation of dietetic foods with regard to its composition and its target group (patients suffering from some sort of nutritive abnormality). A FSMP must differ significantly from a normal food because of its manufacturing process or composition. Finally, the claimed effect must be sufficiently substantiated through experimental evidence and clinical trials standards (aka CTIMPs) that adhere to the regulatory frameworks of the Association of the British Pharmaceutical Industry (ABPI).

There is a need to develop a mechanism through which investigators, industry and the regulatory authorities can work together to better define the regulatory framework for health research relating to nutritional products.

Managing Negative Perceptions and Concerns

The food industry consists of famers, manufacturers (including nutrition, "food as medicine" and "nutraceutical" manufacturers), wholesalers, retailers (which includes supermarkets), distributors and the catering industry. The food industry is a major employer in the UK and, according to a 2010 report from BIS, more people are employed in the food industry in the UK than in any other manufacturing sector. Given the size of this industry together with the need to focus on and improve public health through improved nutrition or diet and lifestyle modifications, and the opportunity that this sector affords in terms of funding research in the UK, working with the food industry will be core to the successful delivery of the vision and aims of the Cancer and Nutrition NIHR infrastructure collaboration.

However, as highlighted in a meeting report from the Centre for Diet and Activity Research (CEDAR): Dietary public health research and the food industry – towards a consensus (December 2015) and summarised more recently in the BMJ (Should we welcome food industry funding of public health research, BMJ 2016; 353: i2161) there are a number of sensitivities around collaborating with the food industry. Some researchers feel that the aims of the food industry and the scientific community are so at odds with each other (i.e. many of the elements of the industry promote and sell food that undermines health) that this leaves scientists who choose to collaborate with the industry vulnerable to publishing biased results or delivering poorly designed or even flawed research. Others feel that there are cases where the interests of the food industry align so strongly with those of health researchers and public health policy more generally (e.g. intervention research on the benefits of micronutrients to health) that there is an opportunity to be grasped. The CEDAR meeting report suggested there needed to be a framework or guidance developed to help define the "rules of engagement" for researchers and the food industry so that all parties, including the public, policy makers and funders could be confident that collaborative studies were unbiased, well designed, of high quality and that all data from these studies be published, in much the same way that collaborative studies with the pharmaceutical industry are now recognised.

Principles of working with Industry.

It is important that, in working with the food industry the Cancer and Nutrition NIHR infrastructure collaboration considers the following points (BMJ 2016):

- Independent researchers, and not the company, should be responsible for the design, conduct and analysis (i.e. study will be designed and delivered by individuals and "research centres/ facilities" who are members of the Cancer & Nutrition NIHR infrastructure collaboration)
- Researchers should have no commercial interest in the product
- Any payments to fund the research should be paid to the institutions not individual researchers, and should reflect the cost of the research (i.e. using the NIHR CRN industry costing template)
- Analysis should be done by statisticians independent of the investigators (i.e. using statisticians identified via the NIHR Statistics Group)
- Researchers should publish the results regardless of the outcome (see NIHR Adding Value in Research Framework).

3. Aims for Working with Industry

By working with the food industry, the Cancer and Nutrition NIHR infrastructure collaboration aims to

- Establish a coherent approach and framework whereby researchers, patients and carers, commercial and industrial partners can work collaboratively to promote, conduct and disseminate best practice in research across NIHR for the benefit of patients and the public.
- bring new and/ or innovative nutritional treatments to those living with and beyond cancer more quickly
- develop new and/ or innovative diet and lifestyle interventions for those living with cancer to help improve their response to treatment (surgery, chemo/radiotherapy), recovery, survival and quality of life
- develop consistent nutrition, diet and lifestyle messaging and guidance for cancer patients and their carers

How Will We Achieve This Vision

Short term objectives (6-12 months):

- Identify NIHR infrastructure with expertise and capabilities to deliver cancer and nutrition research.

- Agree an appropriate mechanism to facilitate collaborative working between the Cancer and Nutrition NIHR infrastructure collaboration (relevant centres) and commercial partners, which is underpinned by agreed ways of working, processes and timelines as appropriate.

Anticipated outputs

- A commitment from NIHR infrastructure centres to form “members” of the collaboration and follow agreed ways for working to deliver collaborative studies with industry, potentially underpinned by an MoU.

Medium term objectives (12-18 months):

- Define the business development plan with clear objectives, tactics for engaging with key industry partners/ industry segments (i.e. scientific conference attendance, engaging with existing contacts, meetings with industry representatives, food industry association meetings, 1-2-1 meetings with appropriately senior individuals/ groups from industry, social media etc) and resources required.

- Identify at least one collaborative project with industry with appropriate funding from commercial partner.

Anticipated outputs

- Business Development Plan in place with appropriate resources to deliver
- One study identified

Longer term objectives (18-24 months onwards):

- Pipeline of developing projects across different industry sectors (e.g. nutraceuticals, supermarkets etc)

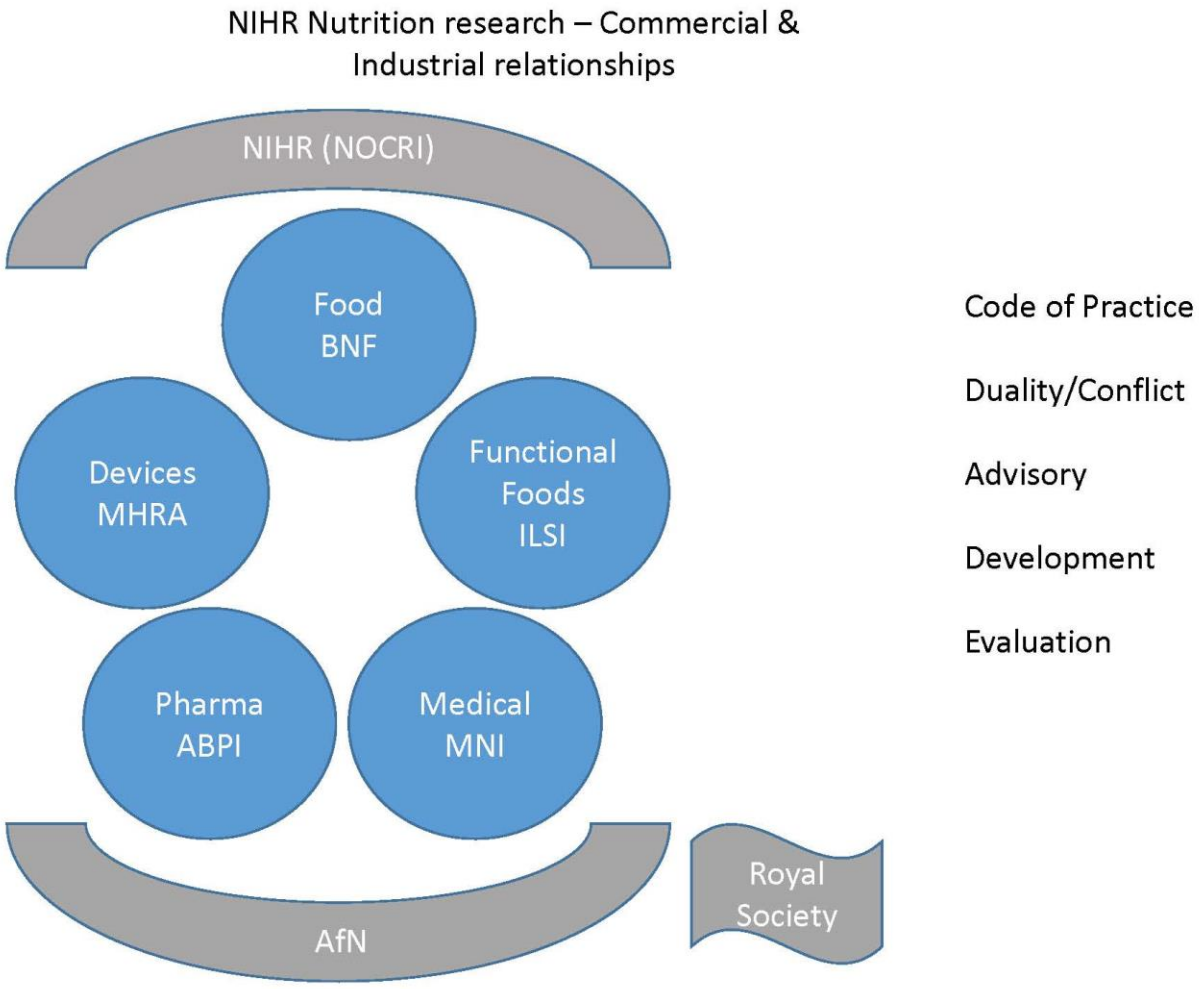

Figure 1. schematic to illustrate key stakeholders by domain in considering Commercial and Industrial relationships.

Appendix 1. Working definitions of terms to describe foods and food products.

Food is any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by human. 'Food' includes drink, chewing gum and any substance, including water, intentionally incorporated into the food during its manufacture, preparation or treatment (Regulation (EC) 178/2002, (Article 2)). Food shall not include…medicinal products within the meaning of Council Directive 65/65/EEC [now Directive 2001/83/EC.]

Foods are consumed to provide nourishment for the body. It is usually of plant or animal origin, and contains essential nutrients, such as fats, proteins, vitamins, or minerals. The substance is ingested by an organism and assimilated by the organism's cells to provide energy, maintain life, or stimulate growth. In addition to compounds recognized as nutrients, food also contains other biologically active (bioactive) compounds that are not deemed essential since the body can function properly without them, but may have an effect in a living organism, tissue or cell.

Functional Foods can be defined as "Natural or processed foods that contains known or unknown biologically-active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease" [Martirosyan and Singh. A new definition of functional food by FFC: what makes a new definition unique? Functional Foods in Health and Disease 2015; 5(6):209-223 Refs].

The BNF see the term 'functional' to describe foods and drinks that are enriched with particular nutrients or substances that have the potential to positively influence health over and above their basic nutritional value. Functional foods are usually similar to foods that are consumed as part of our usual diet e.g. yogurt, drinks, bread. A functional ingredient can be defined as a dietary ingredient that affects its host in a targeted manner so as to exert positive effects that justify certain health claims. In other words, foods containing these ingredients (functional foods) are foods that have health promoting properties over and above their nutritional value. The term 'functional foods' can be viewed as encompassing a very broad range of products, ranging from foods generated around a particular functional ingredient (e.g. stanols-/sterol-enriched reduced/low fat spreads, and dairy products containing probiotic bacteria), through to staple everyday foods fortified with a nutrient that would not usually be present to any great extent (e.g. folic acid fortified bread or breakfast cereals; omega 3 fatty acids from fish oils added to bread or baked beans) (British Nutrition Foundation, Functional Foods. 2016).

The Food Directorate of Health Canada, has proposed that a ***functional food*** is similar in appearance to, or may be, a conventional food, is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions whilst ***nutraceutical foods*** are defined as a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical is demonstrated to have a physiological benefit or provide protection against chronic disease (Nutraceuticals/functional foods and health claims on foods. Policy paper, Therapeutic Products Programme and the Food Directorate from the Health Protection Branch, Health Canada. 1998).

In the EU, ***foods for special medical purposes*** (FSMP) are a sub-category of foods intended for particular nutritional uses (PARNUT), also called "dietetic foods." PARNUT has now been replaced with the Foods for Specific Groups Regulation to ensure a consistent approach across Europe (Regulation (EU) No 609/20130). FSMPs use specially processed or formulated nutritional products intended for the dietary management of patients and to be used under medical supervision. They are intended for the exclusive or

partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary foodstuffs or certain nutrients contained therein or metabolites, or with other medically determined nutrient requirements, whose dietary management cannot be achieved by only modification of the normal diet, by other foods for particular nutritional uses, or by a combination of the two.

In the US, the FDA defined "***medical foods",*** as foods specifically designed and created to facilitate adequate nutrition to people with a certain medical condition that may hinder their ability to consume and/or absorb nutrients, in the 1988 Orphan Drug Act Amendments.

Food or Dietary supplements are legally defined as foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form (Directive 2002/46/EC). This category may include vitamins, minerals, herbs or other botanicals, amino acids, and other dietary substances intended to supplement the diet by increasing the total dietary intake, or as any concentrate, metabolite, constituent, extract, or combination of these ingredients.