Can a probiotics in addition to phytochemical rich foods aid men with indolent prostate cancer?
A randomised double blind placebo controlled trial

Ethics number: IRAS Number: 321309
EudraCT number: Not yet assigned

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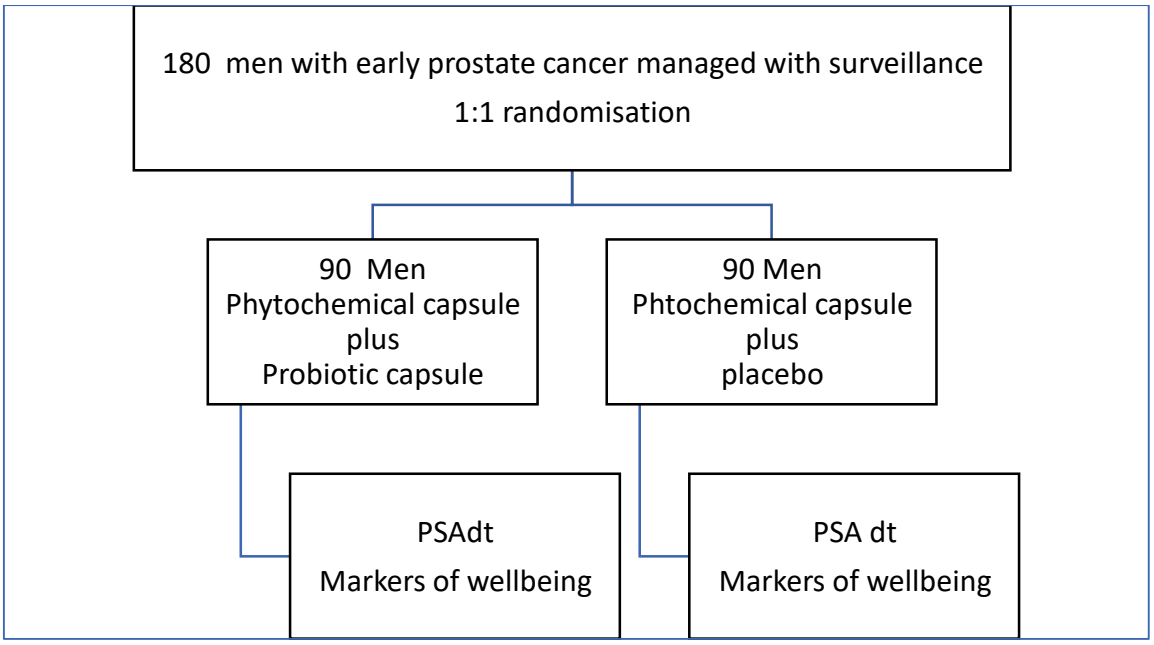
Study summary

Emerging studies are linking poor gut health (dysbiosis) with a greater risk and progression of ca prostate (PCa). Various dietary and lifestyle factors influence dysbiosis but probiotic supplements have also been shown to improve the microbiome floral to a more favourable, less inflammatory profile. Likewise, studies have linked higher intake of phytochemical-rich foods with a lower risk of PCa and Prostatic Specific Antigen (PSA) progression. Phytochemicals have numerous direct and indirect anti-cancer properties, including reducing excess chronic inflammation and enhancing oxidative pathways, but they also act as prebiotics, which support commensal and ingested probiotic bacterial. The hypothesis for this double-blind, randomised trial is that a probiotic supplement could enhance the benefits of a phytochemical-rich supplement via this synergistic effect. A combination of phytochemical-rich food and probiotic supplements has not previously been explored in a cohort of men with PCa, hence the rationale for this study.



Aims: To establish whether boosting the diet with a lactobacillus probiotic in addition to a phytochemical-rich food supplement will influence PSA progression and prostate-related symptoms in men with early PCa compared to placebo.

The intervention: The probiotic capsule will contain 10 billion colony forming units (CFU) of 5 lactobacillus strains with built-in prebiotics. The phytochemical-rich capsule will contain wholefoods which have previously reported potential benefits for men with prostate cancer in epidemiological, laboratory and prospective studies. The ingredients of both supplements have been shown to have a high safety profile.

Cohort: Men with histologically proven, early PCa early not taking androgen deprivation therapy (ADT), managed with active surveillance or watchful waiting.

Methodology: Following written informed consent, all participating men (180) will be given the phytochemical-rich food supplement and asked to stop all other over-the-counter supplements. There will be a double-blind, randomised (1:1) allocation of the probiotic supplement or placebo. The supplements will be taken twice a day for 4 months. Prostatic Specific Antigen doubling time (PSAdt) will be taken at baseline and 4 months together with measures of prostate symptoms and wellbeing.

Background

Since the introduction of testing for serum PSA, the reported incidence of prostate cancer had risen rapidly and this is most prominent in those with less aggressive tumours. Likewise, men with urinary symptoms related to benign prostatic hypertrophy are more likely to receive a PSA blood test, prostatic biopsy and a diagnosis of early cancer, most often low grade.

This expanding group of men, diagnosed with low risk cancer, create a managerial challenge as in this, indolent group, less than 5% will die of their disease and the vast majority are at risk of being over-treated with therapies such as surgery, radiotherapy and brachytherapy. For indolent prostate cancer, many Multiple Disciplinary Teams (MDT) recommend an active surveillance strategy in accordance with National Institute of Clinical Excellence Guidance (NICE), as overall survival is the same as immediate radical intervention [NICE]. This allows many men to avoid or delay the need for radical interventions and hence their associated toxicities. In this group, over 60% report taking over-the-counter (OTC) nutritional supplements, so a confirmatory, new study is welcomed [Uzzo, Bauer].

Lifestyle interventions, which could help delay or prevent the need for radical intervention, are attractive to men not only to avoid treatment toxicities but to empower them in their own management [Thomas, Thomas]. A number of interacting lifestyle factors have demonstrated an influence in prostate cancer outcomes after diagnosis including weight reduction [Gross], smoking cessation [Yu], reducing alcohol intake [Thun, Schoonen], taking regular exercise [Thomas, Hollis, Marshal], but increasing attention is being paid to the importance of diet, particularly foods with a high phytochemical content [Chen, Kolonel, Giovannucci, Giovannucci, Stivala, Block]. These natural chemicals, are responsible for the colour, taste and aroma of healthy foods such as colourful vegetables, fruit, legumes, nuts, herbs, and spices [Thomas, Thomas]. Higher regular intake of these phytochemical-rich foods is linked to lower risks of many chronic disorders ranging from arthritis, type 2 diabetes mellitus and cancer [WCRF/AICR, Key, Scalbert]. Laboratory and clinical studies have highlighted that phytochemicals influence cancer via a number connecting and synergistic pathways:

Reducing chronic, excess Inflammation: Although an inflammatory response is an important part of a healthy innate immunity, persistent low-grade chronic activation of inflammatory pathways is associated with degenerative diseases such as Alzheimer's disease, atherosclerosis and cancer [Lautenbach, Khanasari]. Markers of chronic inflammation are higher among individuals who are older, overweight, sedentary and those with poor diets [Hotamisligil, Franceschi]. One reason for this stems from an overcompensation of an ailing immune system trying to maintain immunosenescence [Franceschi, Khanasari Rukavina]. In this situation, poor interleukin (IL)-2 production leads to a decreased cytotoxic capacity of NK and T lymphocytes on a 'per cell' basis. To compensate, higher levels of inflammatory biomarkers such as C reactive protein, tumour necrosis factor (TNF), IL-6, cytokine antagonists and acute phase proteins are produced which increase concentrations of NK cells and T cells. These transcription factors, as well as promoting inflammatory pathways, affect more than 150 genes involved in mechanisms of cancer proliferation, apoptosis, invasion, angiogenesis and metastases [Hsu, Liu, Ismail, Hotamisligil, Franceschi,]. Fortunately, phytochemicals have been shown to inhibit NF-kappaB signalling in vitro, particularly epigallocatechin-3-gallate (EGCG) and quercetin found in tea and pomegranate;

curcumin, caffeic acid, and caffeic acid phenethyl ester [Salminen, Carlsen, Reuland]. Phytochemical-rich food sources also usually contain natural salicylates which reduce inflammation via COX-2 deactivation of prostaglandins [Hare].

Enhancing anti-oxidant pathways: Some phytochemicals can up regulate anti-oxidant enzymes thereby helping to reduce excess oxidative stress within tissues. This stems from an ability to facilitate activation of the transcription factor NF-E2–related factor 2 (Nrf2), which enhances an appropriate antioxidant response to damaging reactive oxidative species (ROS) [Stivala, Davidson, Juge, Dinkova-Kostova, Khanasari]. ROS are generated at higher levels in obesity after eating carcinogenic foods, following strenuous or excessive exercise [Wang, Chen, Stivala]. Although patients with established prostate cancer have already sustained DNA damage in order to mutate from benign to malignant cells, avoiding further DNA insults may prevent further mutations of indolent malignant, or pre-malignant, cells into more aggressive phenotypes [Chan, Sonn]. Phytochemicals can also promote the natural adaptive to ROS during exercise, yet do not affect the degradation of antioxidant enzymes after exercise, so the time cells spend with optimal oxidative balance is greatly extended [Poljsak, Ristow, Teixeira, Avery, Peternelj, Uchide]. They therefore enhance the safety and health benefits of exercise, important after a diagnosis of cancer [Thomas]. For this reason the term 'anti-oxidant' is misleading when referring to phytochemical-rich foods which, unlike direct anti-oxidant vitamins A and E (highlighted below), do not over deplete ROS levels causing anti-oxidative stress, instead they improve antioxidant efficiency and capacity when needed, and help down regulate it when not needed [Poljsak, Ristow, , Teixeira, Avery, Peternelj, Uchide].

Direct effects: Curcuminoids in turmeric, ellagic acid found in pomegranate and tea have been shown in-vitro to inhibit cancer cell proliferation and induce apoptosis in breast, androgen-sensitive and aggressive human prostate cancer cells [Malik, Ismail. McLarty, Stefanska, Yang, Shah, Dorai, Shanafelt, , Somasundaram, Iqbal, Zhang, Handler, Iqbal]. Pomegranate phytochemicals have also been shown to reduce intracellular markers migration of cancer in both breast and prostate cancer cell lines by increasing cancer cell adhesion [Rettig, wang, Rocha,]. Citrus bioflavonoids found in fruit including pomegranate and cranberries have been shown to inhibit both breast and prostate cancer cell growth by downregulating androgen receptor signalling and promoting G0/G1 cell cycle block and apoptosis [Lee, Vetrichelvan]. In a study involving implanted prostate cancer, xenographs citrus bioflavonoids also down-regulated inflammatory enzymes, inhibited markers of metastasis (matrix metallopeptidase) and reduced angiogenesis via vascular endothelial growth factor inhibition, leading to tumour shrinkage [Lai]. Other animal studies have shown diet rich in citrus fruits protected them from cancer prostate cancer growth as well as testosterone propriated prostatic hypertrophy [Vafa, Tang]. Broccoli, rich in isothiocyanate and sulforaphane, has been shown to inhibit growth and promote apoptosis in cancer cells and animal studies[Sarkar, Beaver, singh]. In humans, studies found that regular broccoli intake down regulated cancer genes linked to cancer growth and up regulated genes linked to cancer suppression [Gasper, Joseph, Sonn].

In humans, the health benefits for phytochemical-rich foods has been highlighted in a number large prospective cohort studies [Block, Key, Heinen, Hu]. This includes meta-analyses which concluded that higher intake of leafy green vegetables and carrots correlated with reduced cancer risk [Tung, Li]. Specific to prostate cancer, prospective cohort studies from across the World have linked diets rich phytochemical-rich colourful fruits such as tomatoes and

pomegranate with a lower risk [Joseph, Giovannucci,]. Four case-controlled studies of cruciferous vegetable intake and prostate cancer risk found that higher cruciferous vegetable intake was significantly lower in men diagnosed with prostate cancer, than men in a cancer-free control group [Cohen, Jain, Joseph]. In one observational study, men eating more than three servings of cruciferous vegetable per week had a 41% reduced risk of developing of prostate cancer than men eating one serving per week or less [Liu]. Additionally, a prospective study found that intake of cruciferous vegetables was inversely associated with more aggressive types or those presenting with metastatic prostate cancer [Kirsh]. An Australian study found that serum levels of phytochemicals were higher in volunteers without prostate cancer compared to men who were recently diagnosed [Dhillon]. Other studies have reported that higher intake of foods, with higher levels of flavonoids such as quercetin, abundant in pomegranate, is associated with a reduced incidence of prostate as well as oesophageal, breast and lung cancers among smokers [Knekt, Arts, Rossi, Le Marchand ,Sun, Vaseghi, Song; Loftfield].

Ginger (Zingiber officinale Roscoe) is rich in several natural bioactive phenolics, including gingerols, paradols, shogaols and gingerones which are known to have anti-inflammatory and antioxidant properties [Thomson, Grzanna, Ojewole, Kim]. Laboratory studies have demonstrated anti-proliferative and apoptosis enhancing effects on human prostate cancer cells [Karna]. The main reason for inclusion is that Gingerols have anti-sickness properties and improve motility of the gastrointestinal tract, which counterbalances any potential aftertaste or slight nausea, as demonstrated in a minority of men in previous supplement studies [Thomas, Boone, Chaiyakunapruk]. Ginger helps improve gut mucous membrane integrity, reducing gut and systemic inflammation, improving a sense of wellbeing, reducing leakage of nutrients out of the body, and yet facilitates absorption and bioavailability of micronutrients and minerals. However, unlike peperine, it does not increase absorption or reduce metabolism of other drugs [Thomson, Grzanna, Ojewole, Dudhatra, Qazi].

The evidence for the benefits of phytochemical-rich foods do not stop after a diagnosis of cancer. Breast cancer survivors who consumed more than the government-recommended five portions of fruit and vegetables a day had a significantly lower risk of breast cancer recurrence [Pierce]. Women with breast cancer who had the highest serum lignan levels, reflecting good intake of legumes, cereals and soy, were reported to have better overall survival than those with the lowest levels [Buck]. The Shanghai Breast Cancer Survival cohort Study, demonstrated that women with the highest intake of the phytoestrogenic polyphenols isoflavone and flavanone, found in soya and other beans, had a significantly decreased risk of breast cancer recurrence and death from any cause compared to those with the lowest intake at a median follow-up of 4 years [Boyapati, Zhu]. Similar findings have been observed for high intake of tea after breast and colorectal cancer [Ogunleye]. A prospective study reported that people, after treatment for skin cancer who had the highest intake dietary phytochemicals from leafy green and yellow vegetables, had a significantly less new skin cancer formation compared with those with the lowest levels of intake [Heinen]. The British Institute of Food Research conducted a prospective study in which men were randomly assigned to either a broccoli-rich or a pea-rich diet. After six months there were significant differences between GST-deficient genotypes on the broccoli-rich diet, associated with transforming growth factor beta 1 (TGFβ1) and epidermal growth factor (EGF) signaling pathways. Comparison of biopsies obtained pre and post intervention, revealed that more changes in gene expression occurred in individuals on a broccoli-rich diet. Men on the broccoli diet had changes to mRNA processing, and TGFβ1, EGF and insulin signaling [Traka].

There are several ways phytochemical dietary intake can be increased, most obviously by eating more colourful, aromatic herbs, spices, teas, vegetables and fruits on a daily basis. Juices and smoothies will further concentrate levels, but this removes the bulk so will increase the glycaemic index (GI) and free sugar content. Concentrating phytochemical-rich wholefoods into a capsule can be a convenient way to supplement total intake and spread it across the day without effecting the GI. Many people living with and beyond cancer are also attracted to the potential health benefits of food supplements, as over 60% are reported to take them regularly [Uzzo, Bauer]. Fortunately, condensing these wholefoods does not usually reduce phytochemical content, which is most often concentrated by the drying process [Agarwal]. It is certainly easier to conduct prospective, interventional studies with supplements, as the quantity and quality of specifical substances can be measured and controlled more precisely. It also allows foods to be blended which have been shown to have synergistic beneficial effects [Khafif].
Cranberry has been investigated in a number of preclinical studies and demonstrated cancer inhibitory potential [Weh]. Clinically, Cranberry extract was investigated in a RCT involving 64 men patients with prostate cancer prior to prostatectomy. In the half who were randomized to a cranberry, compared to those given placebo, there was a statistically significant decrease in PSA, by 22.5%, plus a trend to down-regulation of urinary beta-microseminoprotein (MSMB) and serum gamma-glutamyltranspeptidase, as well as upregulation of IGF-1 [Student].
Another small intervention in men scheduled for radical prostatectomy reported that daily administration of a tea concentrate supplement for seven weeks, caused a reduction in the serum levels of PSA and several cancer-promoting growth factors [McLarty]. A similar design using dried pomegranate extract, for one month, reported a 16% deduction in prostate 8-hydroxy-2-deoxyguanosine (8-OHdG), an oxidative stress biomarker, compared to placebo but was not statistically significant in view of the small numbers of participants [Freedland]. A phase II clinical trial of a supplement containing a dried pomegranate extract slowed PSA doubling time, but a later RCT from the same group using pomegranate juice concentrate did not demonstrate a benefit [Pantuck, Pantuck]. Another trial of concentrated pomegranate juice involving men with castration-resistant prostate cancer also did not demonstrate a benefit [Stenner-Liewen]. A randomised, phase II dose-exploring study carried out at Johns Hopkins did find that men taking a pomegranate extract for 18 months experienced significant reduction in progression of PSA compared to progression rate pre-treatment [Paller]. As a secondary end point, the patients' baseline oxidative state was significantly lower at baseline and after pomegranate consumption, measured by serum induced proliferation and apoptosis of LNCaP cells [Paller]. It appears, therefore, that trials of the juice concentrate have not been successful, but some of studies involving the dried concentration have revealed promising results.

To date, the largest RCT analyzing the effects of concentrated phytochemical-rich wholefood extracts on prostate cance rprogression was published in 2013 [Thomas]. This study combined four different dried foods (pomegranate, green tea, broccoli and turmeric) into a single tablet, taken 2 times a day, and which aimed to provide a wide spectrum of synergistically-acting phytonutrients whilst avoiding over-consumption of any particular phytochemical. The trial involved 203 men with localised prostate cancer, managed with either active surveillance or watchful waiting. The results showed a statistically significant, 63% reduction in median PSA progression rate at 6 months of intervention for the group randomised to the supplement, compared to placebo. A further analysis of the men's MRI scans demonstrated that presence of disease, tumour size and growth patterns on the scans correlated with PSA changes, providing support for the conclusion that the supplement was exerting beneficial effects, not just on PSA

levels, but on the disease itself [Thomas, Thomas]. Furthermore, the supplement was well-tolerated, and there was no effect on testosterone levels. At the end of the study, significantly more men opted to remain on surveillance, rather than proceed to radiotherapy, surgery, or medical castration, saving patients from unpleasant adverse effects [Thomas].

Gut health probiotics and prebiotics

An excess of pro-inflammatory bacteria (dysbiosis), whatever the cause, contributes to gut wall inflammation, reduced mucosal integrity leading to symptoms such as bloating, indigestion and fatigue, as well as an increased risk of both gut and systemic chronic inflammatory and immune related conditions [Nobaek, Lamaudiere, Livingston]. This dysbiosis leads to disruption in the estrobolome (enteric genes that metabolize estrogen), which contributes to the activation polycyclic hydrocarbons in meat leading to the formation of carcinogenic metabolites, inducing cellular DNA damage and leading to carcinogenesis [Katongole, Porter]. Furthermore, the reduced mucosal integrity leaks essential nutrients out of the blood stream, into the gut and at the same time allows toxins to leak into the blood, triggering a systemic, excess inflammatory response [Hakansson]. These factors help explain the link between gut health and cancer, both of the gut and elsewhere in the body, including the prostate [Katongole Porter, Kure]. In support of these data, studies of men undergoing trans-rectal prostate biopsy have reported that those diagnosed with cancer, as opposed to those with benign hyperplasia, or a normal prostate, had a more pro-inflammatory gut bacterial profile [Liss, Golombos, Alanee, Sfanos, Yu].

There is emerging evidence that the development of castration-resistant prostate cancer is associated with changes in the composition of the gut microbiota that favour cancer growth [Pernigoni, Terrisse]. In mice, faecal transplantation from healthy donors, or donors with androgen-sensitive prostate cancer, to mice with androgen resistant prostate cancer, enhanced the response to androgen deprivation therapy (ADT) in some mice; further work is underway to establish the optimal bacterial floral profile [Hsu].

Antibiotics can upset the microbiome, which, in part explains retrospective studies which found that prostate cancer risk increased with regular use of penicillin, quinolones, sulphonamides and tetracyclines [Boursi, Lamaudiere]. In addition to avoiding antibiotics, lifestyle factors which help to maintain a healthy gut microbiome include stopping smoking, reducing processed sugar, exercising more and trying to keep a regular sleep pattern [Devkota, Conlon]. A diverse microbiome can be supported by including foods which contain live probiotic bacteria (such as yogurt, kefir, sauerkraut and kimchi), as well as eating more prebiotic-rich foods (including fermentable soluble fibres such as inulin, oligosaccharides and beta-glucans found in chicory, artichoke, grains, beans and mushrooms), and prebiotic polyphenols found in nuts, onions, fruit pomegranate and herbs [Syngai, Aune].

Some polyphenols and other phytochemicals such as plant lignans found in nuts, ellagitannin found in pomegranate, indole 3-propionic acid found in broccoli and curcumin found in turmeric act as prebiotics to healthy bacteria which helps improve gut health and bowel wall integrity [Gill, Powanda, Alves-Santos, Davinelli, Peron]. The billions of synbiotic bacteria which contribute to the gut microflora prolife, and microbiome as a whole, is increasingly being recognised as an important factor for chronic disease both within, and outside, the gut [Lamaudiere, Sfanos, Golombos, Porter]. Resveratrol in grapes and polygonum cuspidatum root, also enhance the

formation of a protective biofilm over healthy bacteria such as Lactobacillus paracasei, facilitating adhesion, aggregation and colony formation [Al Azzaz, Arcanjo]. Cucuminoids, which are poorly absorbed in the small bowel, pass into the colon where they promote local synthesis of anti-oxidant enzymes, protecting probiotic bacteria from oxidative damage [Arcanjo]. In return, probiotic bacteria help the breakdown of polyphenols into more readily absorbed and more bioactive varieties [Morrison]. Inulin, a soluble, fermentable polysaccharide found in chicory root, passes into the large bowel where it functions as a carbon source for growth favoured by anti-inflammatory commensal bacteria [Dehghan]. Better gut wall efficiency reduces the absorption of proinflammatory toxins into the systemic circulation, avoiding excess systemic inflammation [Powanda, Gross].

Studies have shown that enhancing the diet with a prebiotic supplement could help reduce age-related falls in natural killer cell activity, thereby improving Immunosurveillance both against infection and circulating cancer cells [Gill]. In addition to dietary and behavioural measures, supplementary capsules can increase total intake of pro- and prebiotics, as well as a way to spread their intake throughout the day. The most widely researched probiotics include lactic acid-producing bacteria such as species of Lactobacillus, the colonisation of which is enhanced by concomitant intake with prebiotic soluble fibres such as inulin [Dehghan, Carlson]. Cholecalciferol, even in the small amounts used in this study also acts as a prebiotic [Jones, Jamilian]. Even these low levels, which are unlikely to affect serum cholecalciferol levels, have been shown to help improve gut health by an increased abundance of the mucosal-integrity-promoting bacteria such as the butyrate producers of the Firmicutes phylum [Kanhere, Yoon, Naderpoor, Ciubotaru, Waterhouse, Cantarel, Singh, Jones].

Interventional studies of pro- and prebiotics in humans and animals, have shown that they can help to improve mircrofloral biodiversity, correct GI symptoms and improve immune efficiency [Nobaek. Macfarlane, Azad]. Many of these studies, albeit some needing further confirmation, have shown that they potentially help to modify a range of chronic diseases ranging from long Covid, obesity, inflammatory bowel disease, diabetes, cardiovascular disease, hypertension, anxiety, depression, osteoporosis and dementia [Carlson, Dehghan, Gill, Morshedi, Thomas, Kurian, Thomas].

Despite the laboratory data highlighting the underlying detrimental mechanisms of poor gut health and the links between gut health and prostate cancer, there is a lack of clinical research evaluating the influence of an intervention, which aims to improve gut health, on markers of prostate cancer progression among men with established disease; hence the justification for this study.

Rationale for this design

This design will provide valuable information on whether boosting the diet with a lactobacillus probiotics, in addition to a phytochemical-rich supplement, will help men with early prostate cancer. Although evidence of benefits for phytochemical supplements already exist, further randomised, placebo-controlled trials would provide valuable new data. However, it is likely that patients would be reluctant to enter the study with a possibility of receiving two placebos. Furthermore, it's widely reported that over 70% of men on active surveillance, take one or more

over-the-counter supplements. This wide variability in the type of supplement taken along-side the probiotic, would weaken the reliability data considerably. The best solution would be to ask all participants to stop all other supplements containing any form of whole or extracted food elements. In return, all patients will be supplied with the same supplement to ensure that there is consistency across the entire cohort. If a difference is subsequently found between the randomised groups, it would be less likely that this is influenced by other supplements, and hence be more convincing, and statistically robust, that any differences between the two groups are related to the probiotic.

The International Prostate Symptom Scare (IPSS) and The International Index of Erectile Function (IIEF) have both been validated for routinely used in clinic and are well established for evaluating prostate related symptoms within scientific research studies [Rosen, Selekman].

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Rationale for using these supplements

There are hundreds of commercial probiotics available to use but the rationale for using this particular probiotic complex, is that it meets all the important criteria determined by the scientific committee:

- high quantity of colony forming units (10 Billion CFU)
- built-in prebiotics (Inulin and low dose cholecalciferol), enhance colony formation
- delayed release capsule
- manufactured by a well-established UK manufacturer with high quality certification
- evaluated in previous clinical trials and found to be safe and well-tolerated.

The rationale for using this particular phytochemical-rich blend is that it:

- combines six uniquely different food types, providing a wide spectrum of natural phytochemicals, avoiding over-consumption of one particular type
- combines both whole concentrates and extracts
- minimal levels of candidate phytochemicals are measured and standardised
- contains no foods with phytoestrogen properties
- ingredients have a high safety profile
- manufactured by a well-established UK manufacturer, with high quality certification
- evaluated in previous clinical trials and found to be safe and well-tolerated.

Rational for measuring grip strength

Restricted mobility has consequences for patients with cancer as exercise helps to lower excess systemic inflammation and influence numerous other biochemical pathways, most of which have anti-cancer potential [Thomas, Stark, Wolpin]. This may be one explanation why cohort studies have consistently linked reduced cancer incidence and improved outcomes amongst those able to be physically active after prostate and other cancers [Kenfield, Richman, Ballard-Barbash, Bonn, Friedenreich Chlebowski, Haydon, Schmitz,].

Grip strength is a practical objective biomarker of physical fitness and mobility [Cheung]. Grip strength has been shown to correlate not just with lower arm function but upper limb function, overall strength, bone mineral density, diabetes, fractures and falls [Cheung , Karkkainen , Bohannon]. Grip strength has also been linked to all-cause mortality, future cognitive

impairment, diabetes, depression, sleep problems, hospitalization and quality of life, especially in older adults [Bohannon Abbatecola]. It was even shown to correlate with an increased risk of cancer in the UK biobank study, which followed over 400,000 participants for over 8 years [Parra-Soto]. It has been used successfully in trial involving men with prostate cancer treated with androgen deprivation [Soyupek]. These studies have established that the routine use of grip strength is a useful stand-alone measurement of overall wellbeing in clinical studies [Roberts, Cheung].

Risks, safety and ethical issues

As opposed to some vitamins, minerals and extracted individual phytoestrogenic chemicals, the phytochemical-rich wholefood has a high safety profile [Scalbert]. Most of the ingredients within the supplements proposed for this study have been investigated in previous interventions involving patients with prostate cancer and were very well tolerated [Thomas]. These ingredients were also used in a recent study involving patients with symptomatic Covid-19 infection and also reported a high safety profile [Thomas, Thomas].

Green tea: Millions of people enjoy tea on a daily basis and experience no adverse effects. In very high doses within clinical trials, cancer patients who took 6000 mg/day, in 3-6 divided doses, experienced mild to moderate gastrointestinal side effects including nausea, vomiting, abdominal pain and diarrhoea [Jatoi, Pisters]. Central nervous system symptoms, including agitation, restlessness, insomnia, tremors, dizziness and confusion, have also been reported [Jatoi, Pisters]. The safety of tea extracts or supplements for pregnant or breastfeeding women has not been established. Excessive green tea consumption, theoretically, may decrease the therapeutic effects of warfarin, and such an effect was documented in one patient who began drinking a half-gallon to one gallon of green tea daily [Taylor, Heck].

Broccoli extracts, in high doses, have been found to cause reduce thyroid hormone production in animals [Fenwick]. In humans there has been one case reported of an 88-year-old woman developing hypothyroidism and coma following consumption of an estimated 1.0 to 1.5 kg/day of raw pak choy, over a period of several months [Chu]. On the other hand, one study in humans found that the consumption of 150 g/day (5 oz/day) of cooked Brussels sprouts for four weeks had no adverse effects on thyroid function [McMillan].

Turmeric is a FDA approved food additive and the concentrations used in this study are well within safe limits. Serious adverse effects of turmeric, were not reported even in people taking oral dosages up to 12g for 3 months, in one study from Taiwan [Liao, Cheng]. In a UK study, curcumin supplementation up to 3.6 g/day for four months was generally well-tolerated by people with advanced colorectal cancer, although two participants experienced diarrhoea and another reported nausea [Sharma]. There is no evidence that dietary consumption of turmeric adversely affects pregnancy or lactation. In laboratory studies curcumin has been found to inhibit platelet aggregation in vitro [Shah], suggesting a potential for curcumin supplementation to increase the risk of bleeding in people taking anti-platelet medications, but no reports have been documented in humans. [Thomas, Shah, Sharma].

Pomegranate extracts are very safe apart from rare cases of food allergies. A Johns Hopkins study reported a 14% risk of diarrhoea if doses were over 3g a day, but only a 2% risk if below this dose, as in our proposed study. There are some potential drug inactions because like many fruit juices, pomegranate is a weak inhibitor of cytochrome P450 (CYP2C9). There is, therefore, a small potential risk of reducing the metabolism, and thereby increasing serum levels of warfarin and other coumadins, anti-hypertensives such as captopril, ramipril or anti-convulsants such a carbimazole (www.rxlist.com). Men on warfarin or antihypertensives, however, had no interference of their INR or blood pressure in a previous similar study [Thomas].

Cranberry products are safe unless consumed in very large amounts (greater than 1 litre/day), as they can cause stomach upset and diarrhoea, particularly in young children. Cranberry a very weak inhibitor of cytochrome P450 (CYP2C9). There is conflicting evidence about whether cranberry interacts with the anticoagulant warfarin [Fu].

Ginger is very safe and has tissue-protective properties via its' anti-inflammatory and antioxidant effects [Kaul]. Despite doses of over 500mg in animal studies, no detectable toxicity was reported [Karna].

Probiotics In terms of the safety profile of probiotics, millions of people around the world regularly consume them in supplement form daily, for a variety of perceived health benefits. There are rare instances of excess bacterial overgrowth with prolonged excessive use of probiotics such as E.coli [Rao], but the risk of adverse effects with Lactobacillus use was estimated in one comprehensive French study to be at about one case per 10 million people over a century of probiotic consumption [Bernardeau]. Moreover, the risk of lactobacillemia was considered as 'unequivocally negligible', at <1 case per million individuals in another Italian study [Borriello].

Further evidence for safety was derived from a retrospective study from Finland, which demonstrated that increased probiotic consumption of Lactobacillus rhamnosus GG, did not lead to increased cases of Lactobacillus bacteraemia [Salminen]. Furthermore, clinical studies where certain probiotics have been safely administered to immunocompromised patients with HIV or receiving chemotherapy elderly and patients with Crohn's disease without any side-effects, provide further evidence of poor opportunistic pathogenicity [Bernardeau, Lu]. Probiotics have even been administered to thousands of new born infants, including some who were premature, without a single case of sepsis [Al Faleh]. They have been used in trials involving patients who are severely ill in intensive care, and a recent meta-analysis of 13 RCTs involving potentially immunocompromised patients on chemotherapy, reported a significant reduction in diarrhoea and an improvement in other symptom [NIH]. In another study, a specific blend of lactobacillus was given to patients with a symptomatic Covid-19 infection and 3% reported some increase in bloating and flatulence, but no other adverse events [Thomas]. Given the large quantities of probiotics consumed around the world, the numbers of opportunistic infections that result from probiotic supplements are negligible. For these reasons, the common probiotic species such the *Lactobacillus* used in this trial are very unlikely to cause harm, and this is supported by many international academic bodies [WHO, WCRF, Gibson].

Ingredients:

Phytochemical capsule

(530mg, size 0, cylindrical 21.4mm long):	Equivalent and actual weight (mg)
Whole Broccoli florets and stalks (brassica oleracea)	150 mg
Whole Turmeric rhizome (Curcuma Longa L.)	150 mg
Turmeric extract 50:1 (standardised 95% curcuminoids)	10mg (500 mg, eq)
Whole Pomegranate fruit powder (Punica granatum L.)	150 mg
Pomegranate extract 50:1 (Punica granatum L) (Standardised to Ellagic Acid)	10mg (500 mg, eq)
Green Tea (Camellia sinensis leaves) extract 90% 33.75 Polyphenols 45% EGCG	37.5mg (150 mg, eq)
Whole Ginger *Zingiber officinale* Roscoe	5mg
Cranberry Extract 25:1 2.00 mg	2mg (50 mg, eq)

Inactives (bulking and anticaking agents): Bamboo Extract 75% Silica 10.00 mg, Microcrystalline Cellulose, (Magnesium Stearate, Silicon Dioxide).

Vegetarian capsule Shell: Hydroxypropyl Methylcellulose,

Probiotic capsule (380mg, size 1, 19 mm long):

Colony forming units (CFU):
Lactobacillus rhamnosus 300B CFU/g- Standard 5.55 mg
Lactobacillus plantarum 500 B CFU/ gr- Standard 5.55 mg
Lactobacillus paracasei 300 B CFU/ gr- Standard 835 µg
Lactobacillus bulgaricus 50 B CFU/ gr-Standard 2.775 mg
Lactococcus lactis 200 B CFU/ gr-Standard 835 µg

Prebiotics: Inulin, min 90% inulin-Standard Powder 100 mg, Cholecalciferol 0.1mg

Inactives: Microcrystalline Cellulose Standard Excipient 183.155 mg
Capsule Shell: Vegetarian Hypromellose, Gellan gum 75 mg

Placebo (380mg, 19mm long, size 1):

Inactives: Microcrystalline Cellulose, Magnesium Stearate, Silicon Dioxide).
Vegetarian capsule shell: Hydroxypropyl Methylcellulose.

MHRA considerations

The Medicines and Health Regulatory Agency (MHRA) have been contacted with details of this intervention. They have formally notified the Chief investigator that no MHRA licence is required. This is on the grounds that the intervention is a food and not a drug and, on the basis of this study, no medical products licence will be applied for. (Approval letter is stored in the investigator file)

Objectives of the study

To test whether a nutritional capsule containing lactobacillus probiotic with prebiotics, in addition to a concentrated phytochemical-rich, wholefood supplement, has an influence on PSA progression compared to men taking a phytochemical-rich wholefood supplement alone, among men with prostate cancer, managed with active surveillance or watchful waiting.

Patient population and recruitment process

The trial cohort will consist of men with histologically confirmed prostate cancer managed with active surveillance or watchful waiting, and who are not candidates for immediate therapeutic therapies. All potential participants will have been discussed in their local urology multidisciplinary team (MDT) meeting. Patients meeting the eligibility criteria will be offered written and verbal information about the study during their routine medical consultations or via their specialist nurse. If they are completely satisfied with the information and wish to participate, patients will then be asked to sign the trial consent form before being entered into the study by a member of the research.

Eligibility criteria

Inclusion Criteria

- Histologically confirmed prostate cancer
- Written informed consent
- No current androgen deprivation or other medication for prostate cancer
- Patients who are willing to comply with an oral food supplement
- Patients who are willing to cease all non-trial, over-the-counter oral food supplements
- Patients considered for a surveillance or watch and wait strategy, following multidisciplinary team discussion.

Exclusion Criteria:

- No histological diagnosis of prostate cancer
- Not willing to stop other over the counter supplements
- Patients with liver function tests more than twice the abnormal laboratory range
- Patients with gastric or small bowel malabsorption or dysfunction
- Patients with a known allergy to any of the trial food components.

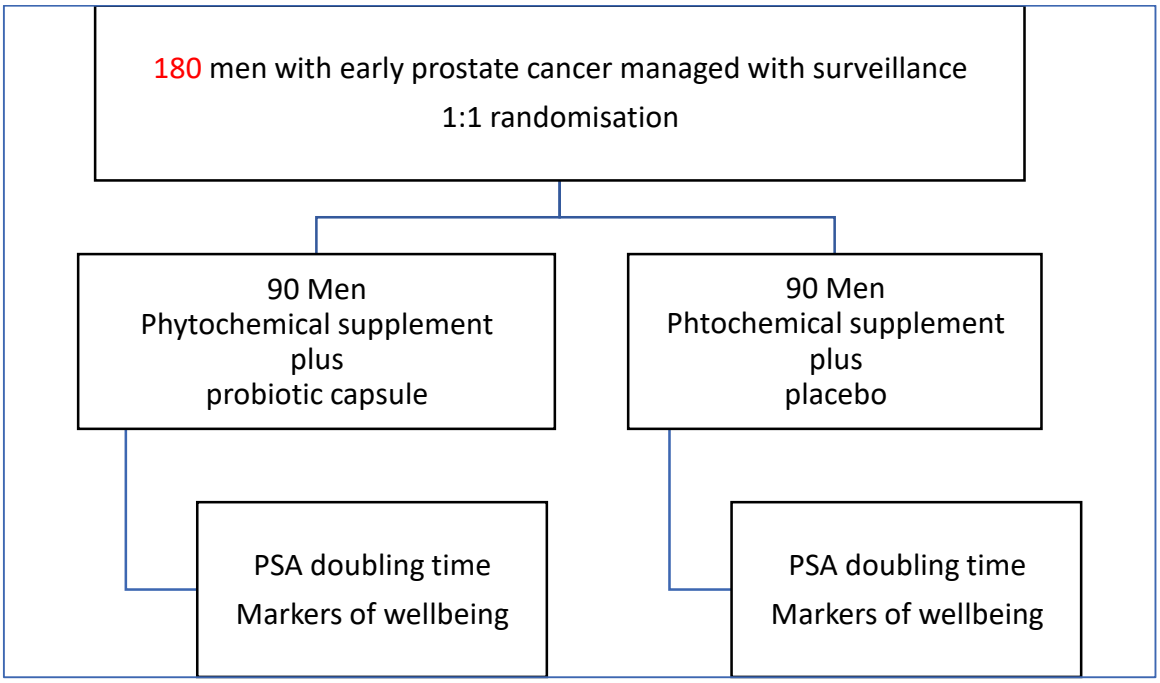
Trial design

This is a double-blind, randomised, controlled trial. Following written informed consent, patients will be randomised (1:1) to:

- Phytochemical food supplement (PFS) plus probiotic
- Phytochemical food supplement plus placebo

Each capsule will be taken twice a day, for 4 months.

Flow Diagram



Trial end points

All variables will be measured at baseline and at 4 months. Difference in variables will be compared between the two randomised groups

Primary endpoint
Serum prostate specific antigen (PSA) doubling time (PSAdt), measured at 4 months, between the two randomised groups

Secondary endpoints (see appendix)
Between the two randomised groups

- International Prostate Symptom Score (IPSS)
- International index of Erectile Function
- Grip strength

Safety measures:
FBC, U&Es, LFTs, serum testosterone, vitamin D. NCI symptom checklist

Pre-determined subgroup for analysis:

Age, ethnicity, BMI

Evaluation schedule

Procedure	Baseline	4 months
Personal data, medical history	X	
Informed consent	X	
PSA	X	X
PSA doubling time*	X	X
FBC, U&Es, LFTs,	X	
FBC, U&Es, LFTs, vitamin D, serum testosterone		X
NCI toxicity checklist	X	X
Concomitant medication (plus supplements)	X	X
Adverse events (at any time during trial)		X
Dispense trial food supplement	X	
Count residual tablets (compliance)		X
IPSS**	X	X
IIEF***	X	X
Grip strength	X	X

* PSAdt measured from baseline to previous PSA; International Prostate symptoms score, **International index of Erectile Function

Study Location

Initially the Primrose Oncology Research Unit, Bedford Hospital, Bedfordshire Hospitals NHS Foundation Trust.

Informed consent

The Principal Investigator will explain to each eligible patient (or legally authorized representative) the nature of the study, its' purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. It will be made clear to each patient that participation in the study is entirely voluntary, and that he may withdraw from the study at any time after giving consent, and that withdrawal of consent will not affect his subsequent medical treatment or relationship with the treating consultant. Patients will be identified by the consultant oncologist supervising their care. Information for the trial will be offered to them during their routine consultation but consent will only be taken after the patient has had time to read and fully understand the information materials.

Trial data recording

Each participant will have a Case Report Form (CRF). Demographics recorded at baseline will include age, Gleason grade, previous treatments, performance status and ethnicity. All patients entered into the study will be included in the efficacy and safety analysis. If a patient was

randomised but failed to, or was subsequently unable to, comply with the trial requirements, the reason for non-compliance and withdrawal will be documented.

Interruption or discontinuation of intervention

It will be documented whether or not each patient completed the trial. If a patient withdraws from the study, the reasons are considered to constitute one of the following:

- adverse event(s)
- abnormal laboratory value(s) related to food supplement
- abnormal test procedure result(s) related to food supplement
- protocol violation
- participant withdrew consent
- lost to follow-up
- administrative problems
- death

Monitoring

The participating centre will be visited by an independent trial monitor to:

- verify information on the case report forms against source data
- review consent forms
- examine any inconsistencies and missing data
- examine the site file for missing data

Statistical plan

At the start of the study and following the final entry, the trial auditor will audit the database trial processes and methodology to ensure adherence to European Good Clinical Practice. All available data from withdrawn subjects will be included in the analysis up to the time of withdrawal. If a patient withdraws before 4 months the PSA at withdrawal will be used for the final analysis. Missing data for PSA will not be replaced. Demographics and other baseline data including age, gleason grade, BMI and PSA will be tabulated for each group and any major imbalance between groups will be taken into account in the analysis. At the end of the trial, the data will be externally audited for a second time to ensure no data inconsistencies or deviation from the trial design has occurred, before being sealed and sent to the external statistician for blind analysis.

All data and efficacy endpoints will be summarised, by randomised group, using descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum). Prior to inferential data analysis, all data will be checked for normality using histograms or via a Smirnov-Kolomogrov test. Homogeneity between the two groups will also be assessed using a Levenes test of homogeneity. For endpoints subjected to formal statistical analysis, the results of the analysis will be summarised and 95% confidence intervals for treatment differences will be presented. All efficacy variables will be analysed for the intention to treat population. The difference in percentage rise between the two groups will be analysed using an independent t-test and an analysis of CoVariance (ANCOVA) and likewise the subgroup analysis will use this test. All significance tests will be two tailed and accepted at $P < 0.05$.

Primary Assessment of probiotic supplement
Null hypothesis (H0) = There will be no significant difference in PSA progression between men taking the phytochemical supplement plus placebo versus phytochemical supplement with the probiotic supplement.

Alternate hypothesis (HA) = There will be a significant difference in PSA progression between men taking the phytochemical supplement plus placebo versus phytochemical supplement with the probiotic supplement.

Secondary assessment
A comparison of PSA doubling time pre-study versus post study (measured at 4 months) for the entire cohort.

A comparison of symptom scores and grip strength baseline to 4 months between to two groups

Sample size and power considerations.
An a priori power calculation (G∗Power3) was used to determine the number of participants Required for this study. At an alpha level of 0.05 and a statistical power of 99%, using published PSA data (PSA at first MRI: 7.3 ± 3.3 μg/l; PSA at second MRI: 9.9 ± 4.4 μg/l) by Thomas et al (2015) it was determined that to detect a moderate effect size change (*d* = 0.66) between the groups that 168 participants in total were required for this study. The allocation ratio between the two groups has been set at 1 resulting in a total of 84 participants to be recruited for each group. To compensate for potential dropouts, a further 6 patients have been added per group, making the final recommended number 180.

Predetermined Subgroup analysis. We will correlate PSA progression with grip strength overall and between the three randomised groups We will compare changes in prostate related symptoms (IPPS) between the two randomised groups.

Blinding; There are two main criteria for blinding. Firstly, the manufacturers will allocate the probiotic capsules and probiotic-placebo as either A or B, without informing the trial centre until the end of the trial and statistical analysis. The phytochemical wholefood capsule will be labelled accordingly. The Chief, Principal and Co-Investigators, trial staff and patients are therefore blind to the probiotic Arm throughout the duration of the trial. Secondly, the statistician, who is independent and remote from the trial centre, will not be given the codes for blinding and will not have encountered participants or trial supplements for the duration of the study. In the unlikely event that un-blinding is necessary for an individual participant, the trial sponsor can be contacted.

Randomisation; Block Randomisation will be employed. A spreadsheet will be created; in column 1, sequential participant numbers will be recorded. In column 2, block-generated randomised Arms (A or B), will be recorded. After a participant has consented they will be allocated the next trial number and randomised Arm in strict order. Participants will be given will be given a four-month supply of either "A" or "B" plus the wholefood supplement.

Confidentiality

On consenting to enter the trial, all data collected will be documented in an anonymous fashion and the subject will only be identified by the trial number and by his/her initials. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, the Investigator is bound to keep this information confidential. Only Bedford Hospital password and fire-wall protected computers will store electronic data. All trial staff will have a valid Good Clinical Practice (GCP) certificate, and the Principal Investigator and Sponsor have attended a Principal Investigator Masterclass workshop. All members of the trials team have completed their data confidentiality training. The trial will be conducted according to the provisions of the Declaration of Helsinki 2013 guidelines and the Date Protection Act 2018.

Safety assessments

The assessment of safety will be based on the frequency of adverse events. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Adverse events Information about adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form, and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study supplement considered to be related to the study intervention. Medical conditions/diseases present before starting the trial are only considered adverse events if they worsen after starting study treatment. As far as possible, each adverse event will also be described by:

1. its duration (start and end dates),
2. the modified NCI toxicity score
3. its relationship to the study drug (suspected / not suspected),
4. the action(s) taken and, as relevant, the outcome.

Serious unexpected adverse events; Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety each serious adverse event must also be reported to Professor Thomas within 24 hours of learning of its occurrence. In view of the nature of the patient cohort and common side effects of chemotherapy, only serious unexpected adverse events will be reported, i.e. an unexpected, undesirable sign, symptom or medical condition occurring which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. was significantly or permanently disabling or incapacitating
4. are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are complications and hospitalizations for:

- Expected complications arising from the underlying malignancy.

- Routine treatment or monitoring not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

Safety reporting responsibility. Any serious adverse event occurring in a patient after providing informed consent and until 4 weeks after stopping the trial must be reported. All serious unexpected adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a patient. Each serious unexpected adverse event must be reported by the investigator to Professor Thomas within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related.

Data handling and recording

Data on subjects collected on CRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, the investigator is bound to keep this information confidential.

All entries to the CRFs must be made clearly in black ball-point pen, to ensure the legibility of self-copying or photocopied pages. Corrections are made by placing a single horizontal line through the incorrect entry, so that it can still be seen, and placing the revised entry beside it. The revised entry must be initialed and dated by a member of the investigator's research team authorized to make CRF entries. Correction fluid will not be used.

The investigator must maintain source documents for each patient in the study. The source documents should contain all demographic and medical information, and a copy of the signed informed consent form which should indicate the study number and title of the trial. All information on CRFs must be traceable to these source documents, which are generally maintained in the patient's file. In cases where there is no prior written or electronic record of data, these data may be recorded directly on the CRFs and be considered as the source data. Such data will be defined in advance of trial start and documented.

Data collection Investigators must enter the information required by the protocol onto the Case Report Forms (CRFs). The project manager will review the CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs are forwarded and stored by Madeleine Williams, Primrose Research Centre, Bedford Hospital, Bedford MK42 9DJ. Once the CRFs are received, their receipt is recorded. Completed CRFs must be signed by the Investigator. An independent auditor will check all data entries and CRF's before submission for statistical analysis.

Changes to the protocol: Any change or addition to this protocol requires a written protocol amendment that must be approved by the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRAS committee.

Ethics and general administration

Declaration of Helsinki The investigator will ensure that the study is conducted in full conformance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong and South Africa).(Appendix 1). The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice", ICH Tripartite Guideline.

Ethics and Regulatory Approval The protocol and any accompanying material will be submitted for approval by the national Research Ethics Committee. Approval must be obtained before starting the study and must be documented in a letter from the NREC.

Approval from the MHRA is not required as the intervention in this study is a food supplement and no application for a drug licence is intended.

Study Termination Both the sponsor and the Investigator reserve the right to terminate the study at any time. The interests of the patients must be considered should termination be necessary.

Investigator File The Investigator must maintain adequate and accurate records in a Study Site File. This should contain as a minimum:

- The protocol and any amendments
- CRF
- Data Query forms
- Ethical committee correspondence and attendees at the relevant meeting
- Investigators Brochure
- CTX approval
- Patient Information and sample Informed Consent
- Staff CVs
- Agreements with the Sponsor
- Agreement from the relevant authorities

Document Retention Subject clinical source documents including all relevant hospital records, laboratory reports, screening and assessment reports, correspondence and signed informed consents must be maintained by the Investigator or assigned to another party for 15 years. All source documents and CRFs are open to inspection by the sponsor and Regulatory Authorities.

Monitoring and auditing An independent trial monitor will be commissioned to evaluate the study and its procedures.

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International prostate symptom score (IPSS)

	Not at all	< 1 time in 5	< half the time	About half	>half the time	Almost always	**score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	

Nocturia	None	1 time	2 times	3 times	4 times	5 times or more	**score**
Over the past month, many times did you most typically getup to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Total IPSS score	

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	equally satisfied dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 Mild symptoms; 8-19 moderate symptoms; 20-35 severe symptoms.

International Index of Erectile Function

These questions ask about the effects that your erection problems have had on your sex life over the last four weeks. Please try to answer the questions as honestly and as clearly as you are able. Your answers will help your doctor to choose the most effective treatment suited to your condition. In answering the questions, the following definitions apply:

- **sexual activity** includes intercourse, caressing, foreplay & masturbation
- **sexual intercourse** is defined as sexual penetration of your partner
- **sexual stimulation** includes situation such as foreplay, erotic pictures etc.
- **ejaculation** is the ejection of semen from the penis (or the feeling of this)
- **orgasm** is the fulfilment or climax following sexual stimulation or intercourse

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OVER THE PAST 4 WEEKS
CHECK ONE BOX ONLY

☐ Q1	**How often were you able to get an erection during sexual activity?**	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q2	**When you had erections with sexual stimulation, how often were your erections hard enough for penetration?**	0 No sexual activity 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q3	**When you attempted intercourse, how often were you able to penetrate (enter) your partner?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q4	**During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q5	**During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?**	0 Did not attempt intercourse 1 Extremely difficult 2 Very difficult 3 Difficult 4 Slightly difficult 5 Not difficult
☐ Q6	**How many times have you attempted sexual intercourse?**	0 No attempts 1 One to two attempts 2 Three to four attempts 3 Five to six attempts 4 Seven to ten attempts 5 Eleven or more attempts
☐ Q7	**When you attempted sexual intercourse, how often was it satisfactory for you?**	0 Did not attempt intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always

☐ Q8	**How much have you enjoyed sexual intercourse?**	0 No intercourse 1 No enjoyment at all 2 Not very enjoyable 3 Fairly enjoyable 4 Highly enjoyable 5 Very highly enjoyable
☐ Q9	**When you had sexual stimulation or intercourse, how often did you ejaculate?**	0 No sexual stimulation or intercourse 1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q10	**When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?**	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q11	**How often have you felt sexual desire?**	1 Almost never or never 2 A few times (less than half the time) 3 Sometimes (about half the time) 4 Most times (more than half the time) 5 Almost always or always
☐ Q12	**How would you rate your level of sexual desire?**	1 Very low or none at all 2 Low 3 Moderate 4 High 5 Very high
☐ Q13	**How satisfied have you been with your overall sex life?**	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q14	**How satisfied have you been with your sexual relationship with your partner?**	1 Very dissatisfied 2 Moderately dissatisfied 3 Equally satisfied & dissatisfied 4 Moderately satisfied 5 Very satisfied
☐ Q15	**How do you rate your confidence that you could get and keep an erection?**	1 Very low 2 Low 3 Moderate 4 High 5 Very high

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF)

Guidelines on Clinical Application of IIEF Patient Questionnaire

Background

The 15-question International Index of Erectile Function (IIEF) Questionnaire is a validated, multi- dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials. A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction.

In a recent study[1],the IIEF Questionnaire was tested in a series of 111 men with sexual dysfunction and 109 age-matched, normal volunteers. The following mean scores were recorded:

FUNCTION DOMAIN	MAX SCORE	CONTROLS	PATIENTS
A. Erectile Function (Q1,2,3,4,5,15)	30	25.8	10.7
B. Orgasmic Function (Q9,10)	10	9.8	5.3
C. Sexual Desire (Q11,12)	10	7.0	6.3
D. Intercourse Satisfaction (Q6,7,8)	15	10.6	5.5
E. Overall Satisfaction (Q13,14)	10	8.6	4.4

Reference

1. Rosen R, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997, **49**: 822-830.