Final Protocol

Title	Randomised double-blind placebo controlled phase II trial of Tocovid SupraBio in combination with pentoxifylline (PTX) in patients suffering long-term adverse effects of radiotherapy for pelvic cancer
Short Title	PPALM - Palm oil and Pentoxifylline Against Late Morbidity
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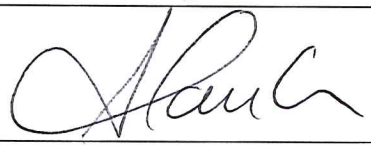
Revision chronology	Effective date	Reason for change
Vs 2, 16.07.2014	20.08.2014	Original REC approval by NRES Committee London-Central
Vs 2.1, 16.07.2015	17.07.2015	Admin error in table showing follow up assessments (page 6 & 5.5)
Vs 3, 4.09.2015	26.10.2015	New information about the concurrent administration of pentoxifylline with Ciprofloxacin (5.8.3). Reference to Adverse Event Log (5.9.4)
Vs 4, 28.01.2016	15.03.2016	Change to withdrawal criteria leaving the decision to CI's discretion (7.5)
Vs 5, 13.09.2016	08.12.2016	New information about the concurrent administration of pentoxifylline with cimetidine and platelet aggregation inhibitors (5.8.3).
Vs 6, 26.06.2017	26.06.2017	Change of CI from Jervoise Andreyev to Alexandra Taylor

Protocol authorised by:	Date	Signature
Dr Alexandra Taylor (Chief Investigator)	26.06.2017	

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SUMMARY OF TRIAL

Aim
To test the benefits of oral Tocovid SupraBio (tocotrienols) with pentoxifylline (PTX) in patients suffering chronic gastrointestinal adverse effects following curative pelvic radiotherapy for cancer.

Trial design
Randomised double-blind placebo-controlled phase II trial.

Eligibility
Specific inclusion criteria:
i) Age over 18 years.
ii) Past history of a malignant pelvic neoplasm (T1-4 N0-2 M0) of the rectum, prostate, testis, bladder, uterine cervix, uterus, vagina, vulva, anal canal or ovary.
iii) A minimum 12 months follow-up post-radiotherapy (24 months for patients with past history of stage T4 and/or N2 disease).
iv) A maximum 7 years post-radiotherapy
v) No evidence of cancer recurrence.
vi) Gastrointestinal symptoms attributable to prior radiotherapy: grade 2 or higher in any CTCAE Version 4 category, or grade 1 with difficult intermittent symptoms.
vii) Symptoms are not relieved by appropriate life-style advice and medication over a 3-month period.
viii) Physical and psychological fitness for Tocovid SupraBio+PTX therapy.
ix) Written informed consent and availability for follow up.
x) Willingness to keep to a specified level of dietary fat intake during the study.

Specific exclusion criteria
i) Surgery for rectal cancer.
ii) Contra-indication or other inability to undergo magnetic resonance imaging, if required to rule out malignancy.
iii) Dietary supplementation containing alpha-tocopherol above a daily dose of 30mg at any time during the last three months.
iv) Medication with pentoxifylline at any time since radiotherapy.
v) Pregnancy or breast feeding.
vi) Ischaemic heart disease, uncontrolled hypertension, hypotension, acute myocardial infarction, cerebral haemorrhage, retinal haemorrhage, renal failure, liver failure and medication with insulin, ketorolac or vitamin K.
vii) Allergy to soya.
viii) Known hypersensitivity to the active constituent, pentoxifylline other methyl xanthines or any of the excipients', as per SmPC for pentoxifylline.

Randomisation
Treatment allocation will be in a 2:1 ratio of Tocovid SupraBio+PTX:Matched placebo and will be based on computer generated random permuted blocks.

Trial treatment
Treatment group
Tocovid SupraBio* 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months.
Control group
Matching placebos bd for 12 months.

*Combination of tocotrienols: d-gamma-tocotrienol + d-alpha-tocotrienol + d-delta-tocotrienol

Endpoints

Primary clinical endpoint

Change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire.

Secondary clinical endpoints

i) Change at 12 months in rectal IBDQ bleeding score between the two groups in those patients presenting with grade 2, 3 or 4 bleeding.
ii) Change at 12 months in IBDQ faecal incontinence score between the two groups in those patients presenting with grade 1 or greater incontinence.
iii) Proportion of items graded as marked or severe (grade 3 or 4).
iv) Physician assessment of rectal dysfunction using the modified CTCAE Version 4 grading.
v) Patient self- assessments: QLQ-C30 and CR29 and the Gastrointestinal Symptom Rating Scale.
vi) Photographic assessments of rectal mucosa.
vii) Serum fibrosis marker levels.

Translational endpoints

i) Rectal biopsies (optional)
Tissue samples will be banked until after the final analysis of the trial, when funding will be sought to identify molecular and cellular correlates of therapeutic response in the event of a statistically significant benefit for the Tocovid SupraBio/PTX combination
ii) Blood samples
Development of novel markers of fibrosis.

Sample size

99 patients will provide 85% power to detect a difference in Modified Inflammatory Bowel Disease Questionnaire bowel subset score of 7.5, which is considered a worthwhile improvement in response to 12 months of Tocovid SupraBio+PTX compared to placebo. 117 patients will be recruited to allow for a 15% drop out rate.

To recommend a patient for eligibility assessments, please contact us by mail, telephone or fax

Dr Alexandra Taylor, Consultant in Clinical Oncology
The Royal Marsden, Fulham Road, London SW3 6JJ
Tel: 020 7811 2581

The following information will be required at referral:

- Referring clinician's full name and address
- Patient's full name, address, date of birth and GP details
- Tumour site, radiotherapy details
- Details of radiotherapy-induced complication
- Details of previous investigations and management

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) as amended. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

PPALM STUDY SCHEDULE OF EVENTS

Procedure	Pre-entry eligibility assessments	Pre-treatment assessments; randomisation and consent	Follow up (months post-randomisation)					
			3	6	9	12	18	24
Clinical assessment	√	√	√	√	√	√		√
CTCAE Version 4 grading	√	√	√	√	√	√		√
Consent procedure		√						
Patient self-assessment questionnaires		√	√	√	√	√	√	√
7 day food diary		√		√		√		
Rectal photographs		√				√		√
Rectal biopsies (optional)		√				√		√
Blood sample		√	√	√	√	√		√
Randomisation		√						

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1 INTRODUCTION

1.1 Radiotherapy has a proven role in the curative treatment of pelvic malignancies

Level I evidence supports the use of radiotherapy to improve local tumour control and long-term survival of patients with carcinoma of the rectum, recto-sigmoid (1-2) and cervix (3-5). There is also level I evidence that radiotherapy contributes to cure in patients with carcinoma of the anus (6-7). At these primary tumour sites, radiotherapy combined with surgery and/or cytotoxic therapy is standard treatment for a high proportion of patients. Radiotherapy alone or combined with cytotoxic therapy and/or surgery is also standard treatment for a high proportion of patients at a number of other important primary tumour sites in the pelvis, including bladder (8-9), prostate (10), vagina (11) and vulva (12).

The global burden of cancer in 2008 was estimated by the Union Internationale Contre Le Cancer (UICCC) to be 12.7 million, of which 3 million comprised cancers of the colorectum, cervix uteri, prostate and bladder (13). Among these, prostate and colorectal cancers represented the second and third commonest cancers in males, and colorectal cancer the second commonest cancer in women (14). Demographic and life-style trends in middle income countries mean that cancer incidence is predicted to rise steeply over the next 2 decades, with the estimated incidence of cancers of the colorectum, cervix uteri, prostate and bladder rising from 3 to 5 million (http://globocan.iarc.fr/). Across the developed world, the total number of patients being treated annually has been estimated to range from 150,000 to 300,000 (15-16) and the use of radiotherapy is increasing rapidly. In the United States, there are estimated to be 2.5 million long-term survivors following pelvic irradiation. Increasing investment in radiotherapy and other cancer treatment facilities in middle income countries means that the number of patients gaining access to curative radiotherapy is destined to rise steeply over the next 20 years (17).

1.2 Radiation-induced gastrointestinal injury causes severe functional disability

Treatment-induced complications are an inevitable consequence of increased local tumour control rates and overall survival, but chronic iatrogenic symptoms exact a high price terms of impaired quality of life (18). Virtually every patient undergoing radiotherapy to the abdomen, pelvis, or rectum develops symptoms of acute bowel toxicity (19-20). The development of late-onset bowel toxicity is related to radiation dose, volume, time and fractionation (21-22) In addition, a poorly characterised dose independent “consequential effect” also contributes as do other treatment and patient-related factors such as diabetes mellitus, hypertension, inflammatory bowel disease and body mass index. The exact degree of risk these factors bring is still debated mainly due to a paucity of adequate studies and a lack of uniformity in methodologies used to define significant late toxicity (15).

Once the acute mucosal reactions have settled, there are broadly speaking four long-term outcomes for patients in terms of bowel function: 10-20% of patients have no long-term sequelae; 30–40% notice some change in bowel habit without any effect on quality of life; in at least 30% of patients, change in bowel function interferes significantly with daily activities and long-term quality of life; finally, a small minority develops life-threatening changes, including transfusion-dependent bleeding, fistula formation, bowel obstruction and secondary malignancy. The incidence of such severe problems is not known precisely, but it is estimated that 4-10% of patients are affected over the first 5-10 years (23-25) and 15-20% over 20 years (26). Although some symptoms may improve with time (27), most chronic syndromes associated with radiotherapy are progressive and irreversible (28). As the number of UK patients

undergoing successful pelvic radiotherapy increases, the morbidity of chronic radiation bowel toxicity becomes more common (19).

The frequency of significant bowel problems cited above is higher than many clinicians recognise. This is because prospective studies using comprehensive, validated methodology concentrating on bowel toxicity with adequate follow up are few in number. Prospective follow up of 77% of 5-year survivors in the Swedish Rectal Cancer Trial testing preoperative high-dose radiotherapy revealed that 30% of the irradiated group had significant impairment of social life due to bowel dysfunction, compared with 10% of the surgery-alone group (29). In another multicentre study which looked at the role of glutamine in protecting against acute radiation toxicity, in which about two-thirds of patients had prostate cancer and most of the rest gynaecological cancer, 2-year follow up was available in 57%. Of these, 12% reported bowel problems moderately affecting daily activity (30). In a third prospective study, a small subset of surviving patients who had undergone adjuvant radiotherapy following surgery for rectal cancer, were compared to a subgroup of patients who had been randomised within the trial to surgery alone. Bowel frequency (80% vs. 23%), loose or liquid stool (60% vs. 23%), fecal incontinence (60% vs. 8%) and need to wear a pad more often (47% vs. 0%) were all significantly more frequent in patients allocated radiotherapy (31).

Physician assessments appear to under-report morbidity. For example, the frequency and severity of gastrointestinal toxicity 18 months post-radiotherapy in a series of prostate radiotherapy trials was 29-45% grade 1, 5-14% grade 2, 0.6-3% grade 3 and 0-1% grade 4 (32-37). However, toxicity was a secondary endpoint and was measured using crude Radiation Therapy Oncology Group (RTOG) external assessments (20, 38-39). A rather different and more sobering picture is obtained from retrospective studies based on patient self-reporting. These studies reveal that patients often do not report toxicity for a variety of reasons (15), and that new bowel symptoms are common and have the greatest impact on quality of life (40). These studies suggest that at least 30% of bladder and gynaecological patients and 20% of all patients treated for prostate cancer have ‘gastrointestinal symptoms causing moderate or severe distress’ as a result of their radiotherapy (41-44). Two other studies using questionnaires proposed for use in the PPALM study found that 50% patients are left with long-term chronic gastrointestinal side effects interfering with daily activity (39, 45). Results in the rectal patients were similar to those described in an earlier detailed case controlled study (46).

1.3 Chronic symptoms and their current management

Twenty three iatrogenic symptoms developing after pelvic radiotherapy have been described (47). These include bleeding per rectum, bloating, constipation, cramps, diarrhoea, faecal incontinence, flatulence, frequency of defaecation, inability to differentiate solid from liquid stool or gas, inability to differentiate need to defaecate from need to pass urine, mucus discharge, nausea, abdominal, rectal, anal or perineal pain, perineal irritation, steatorrhoea, tenesmus, urgency, need for nocturnal defaecation and weight loss. These symptoms in turn lead to major psychological, financial, sexual and social problems.

The management of chronic radiation-induced bowel symptomatology is inadequate. There is seldom a systematic attempt to identify affected patients, few gastroenterologists see many patients and few feel confident to investigate and manage them (15, 48). Several studies have shown that specific symptoms developing after pelvic radiotherapy do not predict the underlying cause for those

symptoms (49-53), yet few patients undergo systematic investigation when they do develop symptoms. If this is carried out, it shows that the majority of patients have more than one cause for their symptoms (15). This may be the reason why the very few trials of treatment have been so disappointing, in that the underlying problems being treated have been so poorly defined (54). The main pharmacological remedy has relied on anti-diarrhoea medicine prescribed to slow bowel transit time and to increase stool consistency. Medication was needed by more than 50% of patients treated with chemo-radiotherapy for rectal cancer in the study by Kollmorgen and colleagues (46). Surgical management is reserved for severe injuries (55). This carries a significant rate of complications, including an operative mortality of 10-21% and a 6-36% incidence of anastomotic dehiscence (56-57). Even after successful surgery, symptoms persist in a significant proportion of patients (57).

However, in our institution we have developed a novel algorithmic approach to manage symptoms. This algorithm has recently been accepted as the standard of care in the UK and endorsed by all major UK professional societies involved in the management of these patients (58). A large randomised controlled trial, the ORBIT study ISRCTN 22890916, testing the efficacy of the algorithm has recently closed and results suggest significant benefit from clinical intervention (unpublished data). Further pilot studies at the Christie hospital using our algorithm have confirmed our findings and suggested an overall improvement in symptoms from targeted intervention of an average of 70% (personal communication). This means that while carefully targeted therapy can be highly effective in ameliorating therapy, residual symptoms are commonplace.

1.4 Vitamin E and pentoxifylline (PTX) in the treatment of delayed radiation injuries

Vitamin E includes all entities exhibiting the biological activity of natural D-α-tocopherol, the most abundant isoform and most widely-used vitamin E supplement (59). The physiological benefits of vitamin E include antioxidant properties, but there are important cellular and tissue responses that cannot be attributed to these properties (60). Therapeutic effects of antioxidants on radiation fibrosis have been tested clinically in a pilot study of intramuscular bovine liposomal Cu/Zn superoxide dismutase (SOD) in patients with superficial fibrosis (61). Supportive data were reported based on topical applications of SOD in patients with skin fibrosis after post-mastectomy radiotherapy (62). In the same period (early 1990's), pentoxifylline (PTX) was reported to have therapeutic potential in patients with radiation adverse effects. PTX is a methylxanthine derivative originally developed for the treatment of regional microcirculation disorders and shown to have anti-inflammatory and immunomodulatory properties. A pilot study in 12 patients with radiation necrosis reported healing in all cases, and a single case report described improvement in pain of radiation fibrosis after only 6 weeks of therapy (63-64). More recently, PTX at a dose of 400mg tds for only 8 weeks in 30 patients with fibrosis 1- to 29-year post-radiotherapy was associated with improvement in functional outcome in more than half the patients and associated with significant falls in plasma FGF2 levels (65). One small randomised (n=40) phase 2 failed to demonstrate improvement in radiation-induced rectal bleeding following 6 months of PTX 400mg bd as single agent (66).

Combined α-tocopherol and PTX therapy has also been evaluated in non-randomised clinical trials of radiation fibrosis and/or necrosis. Early case reports described regression of fibrosis 17 years after postmastectomy radiotherapy in a woman treated with α-tocopherol 600IU(400mg) od and PTX 400mg tds and in a patient with cervico-thoracic fibrosis after radiotherapy for thyroid cancer, in whom x-ray CT evidence of regression was noted (67-68). Regression of superficial radiation

fibrosis after radiotherapy for head and neck cancer or cancer of the breast was recorded in a study of 10 patients treated with α-tocopherol 500IU(335mg) bd and PTX 400mg bd for 6 months, and confirmed in a study of a further 43 patients three years later (69-70). Three months of α-tocopherol plus PTX was reported sufficient to achieve clinical regression of superficial fibrosis in a study involving 29 patients (71). Clinical and magnetic resonance imaging evidence of healing of radiation–induced bone necrosis in a case treated with clodronate plus α-tocopherol and PTX was followed by a phase 2 trial in 18 patients that reported therapeutic benefit in 16 subjects (72-73). The striking lack of randomised evidence was noted by colleagues in Paris, who undertook a double-blind study of 24 patients randomised in a factorial 2 x 2 design to α-tocopherol, PTX &/or placebos (74). Patients were evaluated after 6 months of α-tocopherol/placebo 1000IU (770mg)/day and/or PTX/placebo 1600mg/day with a significant benefit reported for the active combination despite tiny (n=6) subgroups. At other anatomical sites, improvements in symptoms of radiation proctitis/enteritis were reported in a majority of 21 patients treated with α-tocopherol and PTXA (75). Of studies yielding positive outcomes, the best-designed was a placebo-controlled randomised trial (n=83) of PTX/placebo 400mg tds in women prescribed α-tocopherol 100mg (150IU) tds for 12 months starting 1-3 months post-radiotherapy for early breast cancer, which failed to demonstrate benefit for the primary endpoint (shoulder mobility) but attributed a statistically significant (p=0.017) 0.5% difference in arm volume between groups to treatment (76). Not all the published evidence confirms therapeutic effect, including one non-randomised (n=27) study of α-tocopherol 1000IU (670mg)/day and PTX 400mg bd for 6 months in patients with late adverse effects of pelvic radiotherapy (77). A small (n=68) double-blind placebo-controlled trial of α-tocopherol 1000IU (670mg)/day plus PTX 400mg bd for 6 months failed to detect improvement in optical measurement of arm volume in breast cancer patients with radiotherapy-associated arm swelling (78). Negative findings can be criticised on the basis of, among other limitations, too short duration (6 months) of medication (79). Overall, the literature is characterised by non-randomised studies, unreliable endpoints and small sample size. There is a pressing need for appropriately powered randomised studies, which should be double-blind placebo-controlled in view of the subjective nature of most clinical endpoints.

Despite criticisms of the clinical literature, experimental studies in rodents and pigs are consistent with positive clinical findings. An early study of Cu/Zn- and Mn-SOD introduced 26 weeks after a single dose of 160Gy to the thigh of pigs reported striking visual and histological regression of fibrosis in subcutaneous tissue and muscle (69). The same experimental system was used to demonstrate visual and histological evidence of regression of fibrosis in response to α-tocopherol and PTX (80). While these findings are important, they relate to the healing of a very severe acute reaction to radiotherapy, including necrosis. The same limitation may apply to experiments demonstrating therapeutic effects of α-tocopherol and/or PTX introduced 24hr after single doses of 14Gy to the lungs of rats (81). The most convincing data reported significant improvements in selected functional (end-diastolic pressure) and histological (collagens I and III) endpoints in response to α-tocopherol and PTX introduced 3 months after 5 daily fractions of 9Gy to the heart of rats (82).

1.5 Rationale for testing Tocovid SupraBio in combination with pentoxifylline in radiation–induced pelvic injuries

Unsaturated isoforms of vitamin E, including γ-tocotrienol (GT3), are under investigation for their role in maintaining human health and as therapy for several chronic diseases (83). Each of the 4 tocotrienol isoforms have distinct chemical properties beyond those of an antioxidant that are potentially of clinical importance,

including neuroprotective, anti-cancer and cholesterol lowering effects (60). In the context of exposure to ionising radiation, animal studies report the effectiveness of GT3 in protecting experimental animals against acute radiation toxicity. A single dose of GT3 to mice prior to total body radiation increased the LD50/30 (radiation dose lethal in 50% of animals at 30 days post-exposure) corresponding to a dose modifying factor of 1.3 (84). Antioxidant properties may contribute to the radioprotective effects of GT3, but others, including inhibition of HMG-CoA reductase, are postulated to explain endothelial, gastrointestinal and haematological stem cell protection (85-86). So far, no pre-clinical or clinical studies have tested GT3 introduced, alone or in combination with PTX, in the post-radiotherapy period, including at the onset of symptoms and signs of late-onset adverse effects.

Comparative studies of altered gene expression in human endothelial cell cultures treated with GT3 and α-tocopherol report major differences in gene expression, suggesting that GT3 is biologically more potent than α–tocopherol based on the number and nature of transcripts induced (87). GT3 induced 223 gene clusters, compared to only 2 induced by α–tocopherol, including cell death and apoptosis, oxidative stress, responses to DNA damage, cell cycle control, inflammation, blood vessel development and hematopoiesis. Palm oil extracts have been reported to alter the *in vitro* phenotype of fibroblast cultures established from intestinal biopsies of humans with Crohn's disease and ulcerative colitis, reducing proliferative indices and enhancing apoptosis, effects that relevant to potential therapeutic effects following pelvic radiotherapy (88). PTX was reported to enhance the protective effects of GT3 on haemopoiesis, but not gastrointestinal tract, in irradiated mice (89).

1.6 Absorption and bio-availability of tocotrienols in humans

Studies of oral absorption and bio-availability in animals, such as rats, are not predictive for humans, mainly due to differences in intestinal drug metabolizing enzymes (90). Among human studies of oral absorption, a linear dose response for plasma levels of GT3, as for other vitamin E isoforms administered orally, was reported 36 healthy volunteers randomly allocated placebo or a vitamin E formulation (80, 160 & 320mg daily for 2 months) that was 25% GT3 (91). A tocotrienol-rich fraction, prescribed as a commercial palm-based vitamin E consisting of approximately 74% tocotrienols and 26% tocopherol (160 mg/day, including 57.6mg GT3, as a single evening dose), or an identical placebo, was randomly allocated for a period of six months to 62 healthy volunteers, half of whom were aged ≥50 years (92). Plasma lipid-corrected total tocotrienol increased above baseline in subjects aged over 50 years allocated tocotrienols. In a study designed to compare the absorption and metabolism of α-tocopherol and tocotrienols, 10 volunteers on a fat-controlled diet were allocated in a cross-over design with 1-week wash-out period to α-tocopherol 500mg(750IU)/day or a palm tocotrienol-rich supplement containing 526mg(785IU) of vitamin E (167mg α-tocopherol, 157mg α-tocotrienol, 15.2mg β-tocotrienol, 141.8mg GT3, 45.2 δ-tocotrienol) (93). GT3 associated with all plasma lipoprotein factions (diacylglycerol-rich particles, LDL & HDL) increased from zero at baseline to a maximum of 2.73μM (SEM±0.25) at 5 hours, falling to approximately 1μM at 8 hours and to undetectable levels at 24 hours. Potentially therapeutic levels of tocotrienols have been reported in human adipose tissue, brain, heart and liver biopsies following oral administration of supplement tissue biopsies (94). Volunteers receiving a mixed tocotrienol preparation 200mg bd for several weeks prior to surgery recorded mean (+/-SD) tissue levels of 13.3nmol/g ±9.1 in adipose tissue, 5.77nmol/g ±7.72/g in brain, 8.76nmol/g ±5.91 in heart and 6.04nmol/g ±2.27 in liver.

2 PROPOSAL

A double-blind randomised controlled phase II trial of Tocovid SupraBio plus pentoxifylline (PTX) in patients suffering chronic gastrointestinal adverse effects of pelvic radiotherapy.

3 AIM

To test the benefits of oral Tocovid SupraBio (tocotrienols) with pentoxifylline (PTX) in patients suffering chronic gastrointestinal adverse effects following curative pelvic radiotherapy for cancer who have undergone maximal medical therapy after gastroenterological assessment using The Royal Marsden Hospital algorithm for managing GI late effects.

4 PATIENTS

Eligibility will be confirmed by a consultant in gastroenterology at The Royal Marsden with special expertise in the management of late radiation-induced bowel injury.

4.1 Specific inclusion criteria

i) Age over 18 years.
ii) Past history of a malignant pelvic neoplasm (T1-4 N0-2 M0) of the rectum, prostate, testis, bladder, uterine cervix, uterus, vagina, vulva, anal canal or ovary.
iii) A minimum 12 months follow-up post-radiotherapy (24 months for patients with past history of stage T4 and/or N2 disease).
iv) A maximum 7 years post-radiotherapy.
v) No evidence of cancer recurrence.
vi) Gastrointestinal symptoms attributable to prior radiotherapy: grade 2 or higher in any CTCAE Version 4 category, or grade 1 with difficult intermittent symptoms.
vii) Symptoms are not relieved by appropriate life-style advice and medication over a 3-month period after optimal gastroenterological assessment.
viii) Physical and psychological fitness for Tocovid SupraBio + PTX therapy.
ix) Written informed consent and availability for follow up.
x) Willingness to keep to a specified level of dietary fat intake during the study.

4.2 Specific exclusion criteria

i) Surgery for rectal cancer.
ii) Contra-indication or other inability to undergo magnetic resonance imaging, if required to rule out malignancy.
iii) Dietary supplementation containing alpha-tocopherol above a daily dose of 30mg at any time during the last three months.
iv) Medication with pentoxifylline at any time since radiotherapy.
v) Pregnancy or breast feeding.
vi) Ischaemic heart disease, uncontrolled hypertension, hypotension, acute myocardial infarction, cerebral haemorrhage, retinal haemorrhage, renal failure, liver failure and medication with insulin, ketorolac or vitamin K.
vii) Allergy to soya.
viii) Known hypersensitivity to the active constituent, pentoxifylline other methyl xanthines or any of the excipients', as per SmPC for pentoxifylline.

4.3 Pre-entry eligibility assessments

All patients will undergo assessment by a medical specialist and research nurse in the Gastrointestinal Late Toxicity Clinic at The Royal Marsden. Eligibility requires that appropriate life-style advice after optimal gastroenterological assessment and a minimum 3-month period of standard medications are unsuccessful in completely controlling symptoms. Patients will have ample time to consider issues surrounding consent, which will be collected at the time of this appointment.

5 METHODS

5.1 Pre-treatment assessments

The following must be completed *before randomisation*:

i) Patient self-assessments using IBDQ, EORTC Quality of Life Questionnaires (QLQ-C30 & QLQ-CR29) and the Gastrointestinal Symptom Rating Scale.

ii) Physician/Clinical Nurse Practitioner grading of late radiation-induced side effects using the modified CTCAE Version 4 form.

iii) Completion of a 7-day food diary and an interview with the Royal Marsden dietetic team to ensure patients understand as far as possible how to maintain a stable fat intake.

iv) Flexible sigmoidoscopy with rectal biopsies and medical photographs of rectal mucosa (patients who have received prostate brachytherapy will not be eligible for biopsy on grounds of safety). Biopsies will be taken in a standardised manner 8 cm from the anal margin*. Mucosa and a minimal amount of submucosa will be sampled under direct vision. The size of the mucosal deficit caused by the biopsies is 2-3mm and in the patient with radiation proctopathy, this is minimally traumatic. Rectal biopsies (six in total) are optional and will be collected via endoscopy before Tocovid SupraBio+PTX/control therapy in as many volunteers as possible (target is 80% of the whole group). Biopsies will be taken from the posterior third of the rectum. 4/6 samples will be immediately snap frozen in liquid nitrogen for storage. 2/6 samples will be fixed in formalin for future immunohistochemical studies.

v) Blood levels of IL6, TGF beta and MMP9 will be measured as markers of fibrosis. Analysis may be undertaken by researchers outside the Sponsor's organisation including collaborating institutions outside the EU. Any data transferred to a third party for future research will remain coded and will not contain any personal information.

* A pilot study has confirmed that despite the small size of these superficial biopsies, informative samples containing mucosa and some submucosa are easily obtained from irradiated patients using this technique. In further preliminary experiments, we have established that two endoscopically directed biopsies taken from areas of the human rectum showing maximal change from previous radiotherapy are sufficient to obtain adequate amounts of RNA for further analysis.

5.2 Randomisation

Appropriate site staff at The Royal Marsden will randomise patients into the study by a telephone call to the Institute of Cancer Research Clinical Trials & Statistics Unit (ICR-CTSU) on 020 8643 7150. The caller will be given the patient's unique identification number (Trial ID) and treatment allocation will be faxed/emailed to the Pharmacy Department. The Trial ID should be used on all Case Report Forms and all subsequent correspondence relating to that patient.

The following information will be required *at randomisation*:

- Patient's full name, hospital number, date of birth, NHS number.
- Name of hospital/department and person randomising patient.
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist.
- Confirmation that the patient is free of active cancer.
- Confirmation that the patient has given written informed consent for randomisation on the Consent form.
- Whether or not the patient has given written informed consent for rectal tissue biopsies.
- Confirmation that the pre-treatment assessments listed in section 5.1 have been completed, by completion of Pre-randomisation checklist.
- IBDQ-B score (<60 or ≥60).
- Average daily fat intake (<90g or ≥90g).

5.3 Allocation of treatment

Treatment allocation will be in a 2:1 ratio of Tocovid SupraBio+PTX treatment: matched placebo and will be based on computer generated random permuted blocks. Patients will be asked to start their allocated treatment the day after randomisation. Pharmacy will be informed of the randomisation and hold records in the pharmacy file.

5.4 Tocovid SupraBio + PTX therapy

5.4.1 Treatment delivery

Treatment group

Tocovid SupraBio* 200mg po bd plus pentoxifylline (PTX) 400mg po bd for 12 months.

Control group

Matching placebos po bd for 12 months.

*Combination of tocotrienols: d-gamma-tocotrienol + d-alpha-tocotrienol + d-delta-tocotrienol

5.4.2 Monitoring of patients during treatment

i) Adverse events will be recorded and reported as appropriate.
ii) Any patient can be withdrawn from the study at any time.
iii) Reasons for withdrawals and any adverse events will be documented and considered in the analysis.
iv) Patients will be asked to produce a list of current medication (including dosage) before they enter into the study and to keep a medication diary during their Tocovid SupraBio + PTX/placebo therapy. Changes in medication during the 12

months of follow up will be collected at the assessment 24 months post randomisation.

v) Levels of plasma GT3 will be measured at baseline, 3, 6, 9 and 12 months to confirm compliance with drug in those randomised to Tocovid SupraBio/PTX and undetectable levels of GT3 in those allocated placebo. Appropriate Royal Marsden site staff will check compliance in clinic from diary card kept by patients and any leftover trial medication (if applicable).

5.5 Follow up assessments during and after treatment (please see table below)

i) Patient self-assessments using IBDQ, the EORTC Quality of Life Questionnaires (QLQ-C30 & QLQ-CR29) and the Gastrointestinal Symptom Rating Scale 3, 6, 9, 12, 18 and 24 months after randomisation.

ii) Physician/Clinical Nurse Practitioner grading of late radiation-induced side effects using the modified CTCAE Version 4 form 3, 6, 9, 12 and 24 months after randomisation.

iii) Re-assessment with a 7-day food diary at 6 months and 1 year.

iv) Flexible sigmoidoscopy with rectal biopsies (optional) and medical photographs of rectal mucosa 12 and 24 months after randomisation.

v) Blood levels of IL6, TGF beta and MMP9 3, 6, 9, 12 and 24 months after randomisation as markers of fibrosis.

Procedure	**Follow up (months post-randomisation)**					
	3	**6**	**9**	**12**	**18**	**24**
Patient self-assessment questionnaires	√	√	√	√	√	√
CTCAE Version 4 grading	√	√	√	√		√
Clinical assessments	√	√	√	√		√
7 day food diary		√		√		
Rectal photographs				√		√
Rectal biopsies (optional)				√		√
Blood sample	√	√	√	√		√

5.6 Processing and storage of tissue

5.6.1 Rectal tissue biopsies

Tissue samples a) snap frozen and stored in liquid nitrogen or b) fixed in formalin and embedded in paraffin blocks will be stored for future immunohistochemical analyses of blood vessel density and extracellular matrix components.

5.6.2 Blood samples

Blood samples will be collected into EDTA tubes and stored to develop assays for novel markers of fibrosis.

5.7 Endpoints

5.7.1 Primary clinical endpoint

Change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire.

5.7.2 Secondary clinical endpoints

i) Change at 12 months in rectal IBDQ bleeding score between the two groups in those patients presenting with grade 2, 3 or 4 bleeding.
ii) Change at 12 months in IBDQ faecal incontinence score between the two groups in those patients presenting with grade 1 or greater incontinence.
iii) Proportion of items graded as marked or severe (grade 3 or 4).
iv) Physician assessment of rectal dysfunction based on the modified CTCAE Version 4 grading.
v) Patient self-assessments: QLQ-C30 and CR29 and the Gastrointestinal Symptom Rating Scale.
vi) Photographic assessment of rectal mucosa.
vii) Serum fibrosis marker levels.

5.7.3 Translational endpoints

i) Rectal biopsies (optional)
Tissue samples will be banked until after the final analysis of the trial, when funding will be sought to identify molecular and cellular correlates of therapeutic response in the event of a statistically significant benefit for Tocovid SupraBio/ PTX combination.
ii) Blood samples
Development of novel markers of fibrosis.

5.8 STUDY MEDICATION

5.8.1 Investigational Medicinal Product

The investigational medicinal products are as follows:

i) Pentoxifylline 400mg capsules and Pentoxifylline matching placebo
ii) Tocovid SupraBio 200mg capsules and Tocovid SupraBio matching placebo

Pentoxifylline tablets used will be sourced by Mawdsley Brooks Ltd, UK from member states of the EU. To maintain study blind, the EU licensed pentoxifylline tablets will be encapsulated and matching placebo capsules manufactured under EU GMP conditions by Mawdsley Brooks Ltd (or designated authorized manufacturing contractor).

Tocovid SupraBio soft gel capsules are considered a dietary supplement. Tocovid SupraBio capsules and matching placebo will be manufactured, packaged and labeled in accordance with EU GMP by Hovid Bhd, Malaysia. The manufacturing, packaging and labeling sites have been audited and assessed to ensure EU GMP compliance. An EU QP declaration equivalence to EU GMP for IMP manufactured by Hovid Bhd is provided with the trial application.

5.8.2 Preparation and Administration of Study Drug

Packaging & Labelling
All IMPs including placebos will be imported (where applicable), certified and released for use in this study by Mawdsley Brooks Ltd. IMPs will be packaged, labelled and dispatched to investigator site as agreed as open label supplies.
The Pharmacy department at The Royal Marsden will label study medication against prescriptions in accordance with requirements specified in Annex 13 of the Eudralex volume 4 and ensure that blinding is maintained.

Receipt of Drug Supplies
Drug supplies will be shipped directly to the pharmacy department. Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

Storage
Pentoxifylline/placebo and Tocovid SupraBio/placebo must be stored as per the product label. IMPs should be stored in the pharmacy and segregated from normal pharmacy supplies.

Blinding of Study Drug
Pharmacy will be unblinded in the study and will dispense appropriate IMPs as per randomisation confirmation received from ICR-CTSU (see section 5.2). All paperwork relating to identity of patients on active or placebo will be held in the pharmacy file, separate from the TMF held by the research team. Pharmacy will order supplies directly from Mawdsleys as per agreed process, without involvement from the investigator and research team.

Emergency Unblinding
In the case of emergency unblinding, the pharmacy department will hold a list of all patients registered onto study and treatment arm patients are randomised to. Pharmacy has a 24 hour oncall service and will be available to unblind in emergency situations as appropriate and as per local procedures.

Treatment Compliance
Patient's treatment compliance will be assessed by appropriate Royal Marsden staff in the clinic. Patients will be asked to bring all empty packaging/unused tablets at each clinic visit.

Drug Accountability and Destruction
The investigator will delegate responsibility for IMP management to the delegated pharmacist. Full drug accountability from receipt to destruction will be held in pharmacy for all IMPs. The delegated pharmacist will also ensure:

- IMPs are handled and stored safely and properly.
- IMPs are only dispensed to trial patients according to the protocol.
- IMPs will be destroyed (expired stock, patient returns, left over stock at end of study) as per local procedures in liaison with R&D and CI.
- Blinding of IMP prior to release to patient and research team.

5.8.3 Concomitant Medication

Disallowed medicines include:

- Ketorolac
- Insulin
- Vitamin K

Caution should be used with the following medicines in combination with pentoxifylline;

- Theophylline – can lead to increased levels of theophylline therefore increased therapeutic drug monitoring required
- Anti-coagulants – risk of increased anticoagulant activity
- Anti-hypertensives – PTX may potentiate the effects of anti-hypertensive agents.
- Ciprofloxacin - Concomitant administration with ciprofloxacin may increase the serum concentration of pentoxifylline in some patients. Therefore, there may be an increase in and intensification of adverse reactions associated with co-administration.
- Platelet aggregation inhibitors - Potential additive effect with platelet aggregation inhibitors: Because of the increased risk of bleeding, the concomitant administration of a platelet aggregation inhibitor (such as clopidogrel, eptifibatide, tirofiban, epoprostenol, iloprost, abciximab, anagrelide, NSAIDs other than selective COX-2 inhibitors, acetylsalicylates (ASA/LAS), ticlopidine, dipyridamole) with pentoxifylline should be undertaken with caution.
- Cimetidine - Concomitant administration with cimetidine may increase the plasma concentration of pentoxifylline and the active metabolite, lisofylline.

Dose Reductions

No dose reductions are permitted of any IMPs.

5.9 Safety Reporting / Pharmacovigilance

5.9.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a study drug, whether or not considered related to the study drug. Signs and symptoms of metastatic disease, as determined by the local clinical investigator, are not adverse events.

Adverse Reaction (AR):

All untoward and unintended responses to the study drug related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions i.e. an AR is possibly, probably or definitely related to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR):
Any untoward medical occurrence or effect which occurs within 30 days of the patient receiving study drug that at any dose:

- results in death: the patient's death is suspected as being a direct outcome of the AE.
- is life-threatening. Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- requires hospitalisation, or prolongation of existing inpatient hospitalisation: admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE. Outpatient treatment in an emergency room is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study.
- results in persistent or significant disability or incapacity: the AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- is a congenital anomaly or birth defect.

N.B. progressive disease and death due to disease are not considered SAEs but should be reported on the relevant forms (i.e. progression form for relapse and death form for death).

Medical judgement should be exercised in deciding whether other AE/ARs are serious. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious and reported as such.

Suspected Unexpected Serious Adverse Reaction (SUSAR):
Any serious adverse event with a suspected relationship to study drug that is not listed on the SmPC (Pentoxifylline) / IB (Tocovid SupraBio) and is unexpected.

Causality
Many adverse events that occur in this trial, whether they are serious or not, will be known treatment related toxicities. The Chief Investigator is responsible for the assessment of causality of serious adverse events (see definitions of causality table). The drug manufacturer and/or other clinicians may be asked for advice.

Definitions for causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after

	administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

5.9.2 Reporting procedures

Reporting of Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any SAE that occurs from the time of consent and up to 30 days following the last dose of the study medication must be reported. The Sponsor has delegated safety reporting to the Chief Investigator. Since this is a single-centre trial, the CI is also the PI. Any member of the research team who becomes aware of an SAE shall report the SAE to the CI using the SAE report form immediately and no later than 24 hours from site awareness of the event. The SAE will be assessed by the CI for causality and expectedness. The signed SAE form should be kept in the TMF. SAEs and SARs will also be recorded on the Sponsor's Pharmacovigilance Database in compliance with The Royal Marsden NHS Foundation Trust standard operating procedure for Pharmacovigilance gSOP-02.

Reporting of SUSARs
All reporting of SUSARs will be done in compliance with the Royal Marsden NHS Foundation Trust current standard operating procedure.

If an SAE is identified as being a SUSAR by the CI, and is fatal or life threatening, it will be reported by the CI to the MHRA, the REC and the Royal Marsden R&D Office within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the CI, and is not fatal or life threatening, it will be reported by the CI to the MHRA, the REC and the Royal Marsden R&D Office within 15 days of knowledge.

The CI will report any additional relevant information to the MHRA, the REC and the Royal Marsden R&D Office as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

Serious Adverse Event follow up
The subject must be followed-up until clinical recovery is complete, laboratory tests have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SAE which may not be available at the time the SAE is initially reported should be forwarded to the CI.

DSURs and Annual Progress Report
The CI is responsible for producing an annual DSUR in liaison with the Pharmacovigilance Officer in the Trust Clinical R&D office, which will be sent to the MHRA. An Annual Progress Report will be submitted to the Research Ethics Committee.

5.9.3 Expected adverse events

Pentoxifylline: The drug is generally well tolerated, but the following adverse effects have been listed: abnormal laboratory test results; anaphylactic reactions seek; immediate medical advice if you get an anaphylactic reaction; angina; angioedema; bleeding; bronchospasm; diarrhoea; distension of the stomach; faster heart rate; feeling agitated; feeling dizzy; gastrointestinal problems; headaches; hot flushes; irregular heart rate; itching; liver problems; lowered blood pressure; meningitis or meningitislike symptoms; nausea; redness of the skin; sleeping problems; stomach discomfort; thrombocytopenia; urticaria; vomiting
(The frequency of these side effects is unknown. Ref: emc Medicine Guides 28 Jun 11).

Tocovid SupraBio: There are no known side effects from Tocovid Suprabio at the dose prescribed in this study.

5.9.4 Recording of adverse events

All adverse events will be documented on the PPALM Adverse Event Log and entered onto the trial database.

6 STATISTICAL CONSIDERATIONS

6.1 Stratification

Patients will be stratified according to:

i) the severity of their symptoms (IBDQ-B ≥60 vs. IBDQ-B <60)
ii) average daily fat intake ≥90g fat/day vs. intake <90g fat/day

6.2 Principal Endpoint

6.2.1 Primary endpoint

Change at 12 months in the bowel disease subset of the Modified IBDQ Quality of Life questionnaire.

6.2.2 Secondary endpoints

i) Change at 12 months in rectal IBDQ bleeding score between the two groups in those patients presenting with grade 2, 3 or 4 bleeding.
ii) Change at 12 months in IBDQ faecal incontinence score between the two groups in those patients presenting with grade 1 or greater incontinence.
iii) Proportion of items graded as marked or severe (grade 3 or 4).
iv) Physician assessment of rectal dysfunction using the modified CTCAE Version 4 grading.
v) Patient self-assessments: QLQ–C30 and CR29 and the Gastrointestinal Symptom Rating Scale.
vi) Photographic assessments of rectal mucosa.
vii) Serum fibrosis marker levels.

6.3 Sample size

Sample size estimation has been based on changes in the Modified Inflammatory Bowel Disease Questionnaire bowel subset score.

Primary endpoint

We have previously shown that the IBDQ-B (Inflammatory Bowel Disease Questionnaire is a more sensitive tool than the more commonly used RTOG (Radiation Therapy Oncology Group) and LENT SOM scoring tool (20). It is a questionnaire developed and validated for patients with chronic inflammatory bowel disease, in whom changes in score associated with improved, stable or worsening symptoms have been reported (95). The whole questionnaire is scored out of 224 and gives a bowel health and overall quality of life score. The bowel subset of the IBDQ is scored out of 70, using data from 10 of the 32 questions. Mean (±SD) changes in IBD questionnaire bowel subset score were 15 ±10 for n=109 with improving symptoms, 3 ±7 for n=63 with stable symptoms and -3 ±6 for n=8 with worsening symptoms. In the PPALM trial, 10 will be used an estimate of the standard deviation (SD) of the change at 12 months. A difference in questionnaire score of 7.5 is selected as representing a clinically worthwhile improvement in response to 12 months of Tocovid SupraBio+PTX compared to placebo. We therefore need 99 patients (66 GT3+PTX:33 placebo) for 85% power employing a two-sided 1.67% significance level. We have adopted this level of significance because we wish to keep a 5% overall false positive rate after inclusion of the secondary endpoints relating to changes in bleeding and faecal incontinence.

Secondary endpoints

We estimate that 40% of patients will have grade 2, 3 or 4 bleeding, based on our ongoing trial evaluating hyperbaric oxygen in a comparable group of patients, comprising 39 of the 99 patients. The reduction in bleeding in this group of patients will be compared between randomised groups. A reduction in the true proportion of patients showing a fall in their grade of rectal bleeding at 12 months from 70% showing a fall (i.e. 7 in 10) in the Tocovid SupraBio+PTX group to 10% in the placebo group would be detectable (80% power, 1.67% two sided significance level). The pattern of rectal bleeding change in the patients with grade 0-1 bleeding at baseline will be reported but not formally compared between arms. This group is of less interest because mild bleeding does not represent a major impediment to daily living and these individuals are very unlikely to develop serious rectal bleeding over the period of the trial.

We expect that 70% of patients will have grade 1 (35%) or 2 (35%) faecal incontinence, based on the same trial evaluating hyperbaric oxygen, comprising 69 of the 99 patients, and this subgroup can be used to examine the reduction in incontinence. A reduction in the true proportion of patients showing a fall in their grade of faecal incontinence at 12 months from 55% in the Tocovid SupraBio+PTX group to 10% in the placebo group would be detectable (80% power, 1.67% two sided significance level). The pattern of faecal incontinence change in the patients who are grade 0 at baseline will be reported but not formally compared between arms.

The combined false positive rate for the three endpoints described above is 5% (3 x 1.67%).

Our aim is 99 evaluable patients, and 117 patients will therefore be recruited to allow for a 15% drop out rate.

6.4 Analysis

Primary endpoint

Analysis of the bowel function component of the Modified Inflammatory Bowel Disease questionnaire is the primary endpoint, and analysis will be carried out on an intention to treat basis. The mean difference in change from baseline to 12 months in both trial arms will be compared using the Mann-Whitney U test, or unpaired t-test if the values are approximately normally distributed. If necessary, multivariate analysis will be used to adjust for any potential confounding factors, though the ability to use multivariate analysis will be limited by the fact there are only 33 patients in one arm. The impact of missing values will be investigated by using techniques such as LOCF.

Secondary Endpoints

The proportions of patients showing a change in rectal IBDQ bleeding score and Faecal incontinence score will be compared using Fisher's exact test.

There will be no formal statistical analysis of the other secondary endpoints but the descriptive nature of these results will be used to strengthen the interpretation of changes in the primary endpoint. Several analyses will be carried out including but not limited to the following:

i) Changes in modified CTCAE Version 4 grades.
ii) Standard procedures will be followed for describing quantitative changes in QoL domains using EORTC Quality of Life Questionnaires (QLQ-C30 and CR29).
iii) Photographs of rectal mucosa will be scored by two experienced endoscopists, who will be blinded with respect to treatment allocation and time of assessment (pre- or post-treatment). The mucosal appearance will be scored using the Wachter classification (51). Disagreement in any scores will be resolved by arbitration after discussion with a third independent endoscopist. Differences in the appearance before and after treatment between the two groups will be assessed.
iv) Change in levels of 3 serum markers of fibrosis.

6.5 Frequency of analyses

There will be a sequential monitoring of toxicity, and the first analysis will be carried out when the first 21 patients have completed the first 12 months of assessment. Toxicity and the frequency and nature of adverse events will be compared between the randomised groups. Summary measures and non-parametric tests will be used as necessary. In particular, the proportion of patients experiencing toxicity grade 3 or 4 and the maximum toxicity grade will be compared. An analysis of safety endpoints by treatment received will be performed.

7 RESEARCH GOVERNANCE

7.1 Trial Administration and Logistics

The Royal Marsden NHS Foundation Trust is the agreed Sponsor of this study in accordance with the Medicines for Human Use (Clinical Trials) Regulation 2004 as amended and in line with the Research Governance Framework for Health and Social Care and the principles of Good Clinical Practice (GCP).

7.1.1 Chief Investigator responsibilities

The Chief Investigator has overall responsibility for facilitating and coordinating the conduct of the trial.

7.1.2 Responsibilities of ICR-CTSU

ICR-CTSU has responsibility for storing the clinical trial data and undertaking and reporting interim and final analyses.

7.2 Case Report Forms (CRFs)

A series of questionnaires will be completed by both the patient and research team at set time points during the study in order to assess the patient's late radiotherapy side effects and quality of life. The CRFs completed in clinic should be signed and dated and forwarded to the Trial Coordinator once completed. The Trial Coordinator will review incoming CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant Royal Marsden staff for resolution. Following initial review, the Trial Coordinator will enter the CRF data items into the clinical study database held at ICR-CTSU.

The CRFs will not be made available to people outside of the research team, however, access will be granted for audit and monitoring purposes and will be provided to regulatory authorities, Research Ethics Committee or other relevant ICR or Trust personnel.

7.3 Protocol compliance

This trial is being conducted in accordance with applicable statutory and regulatory requirements and guidelines for non-commercial research in the NHS under the EU Clinical Trials Directive.

7.4 Treatment compliance/deviation

It is the responsibility of appropriate Royal Marsden site staff to complete a Treatment Compliance Form for each patient who is randomised to the trial.

If the patient does not receive their treatment as per the trial protocol, the Royal Marsden site staff must also complete a Deviation Form.

If a patient's condition deteriorates during Tocovid SupraBio+PTX therapy, and their GP requires them to be hospitalised for investigations and treatment, they can be temporarily removed from the trial. Tocovid SupraBio+PTX therapy in accordance with their original randomisation will be resumed on completion of the referral, unless the GP decides against this in liaison with the CI. A copy of the Deviation Form as well as Treatment Compliance Form must be completed for such patients.

All completed forms should be signed and sent via hard copy or email to the CI, Dr Alexandra Taylor, Consultant in Clinical Oncology, The Royal Marsden, Fulham Road, London, SW3 6JJ. Tel: 020 7811 2581. Email: alexandra.taylor@rmh.nhs.uk

7.5 Treatment withdrawal

Patients must be withdrawn from the study for the following reasons:

- Disease progression before completion of study treatment*.
- Withdrawal of consent for treatment and/or study participation.

- Unacceptable treatment related toxicity or adverse events as judged by either the patient's GP or the Chief Investigator.
- Pregnancy.
- Patient non-compliance.
- Death.

*If a patient satisfies the criteria for treatment withdrawal based on disease progression but is deemed by the Chief Investigator (CI) to be benefitting from treatment (e.g., symptomatic relief), such a patient may remain on the trial (i.e., continue receiving IMP and undergoing trial assessments) until such a time when the CI determines it no longer beneficial to do so.

7.6 Direct Access to Source Data

On a day to day basis only members of the research team will have direct access to data and documents pertaining to this study. Access for audit purposes will be provided to regulatory authorities, Research Ethics Committee or other relevant ICR or Trust personnel.

The Case Report Form will be considered source data for this study as the forms are questionnaires completed directly by patients and/or clinical staff. Thus the information will not be recorded in the medical notes or on the Hospital Information System. However, consent and eligibility should be documented in the medical notes and this will be checked at random as part of the monitoring for this study.

Key eligibility components to be recorded on the Royal Marsden Electronic Patient Record System.

7.7 Trial Management

7.7.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified Collaborators, the Trial Statistician, Clinical Nurse Practitioner and the Trial Co-ordinator. Key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial.

7.7.2 Trial Steering Committee

A Trial Steering Committee (TSC) will monitor and supervise the progress of the trial. The role of the TSC is to provide overall supervision of the trial on behalf of the funding body. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and the consideration of new information. Day-to-day management of the trial is the responsibility of the Chief Investigator and TMG.

Membership will be limited and include an independent Chair (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, the Chief Investigator and the Trial Statistician.

The Trial co-ordinator and other key members of the TMG will attend meetings (as observers) as appropriate. Observers from the funding body and, if applicable, host Institutions or sponsors will be invited to all meetings. The TSC will meet at least annually.

7.7.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to oversee the safety and interim efficacy of the trial. This committee will be constituted according to MRC Good Clinical Practice (MRC GCP). The IDMC will meet on a regular basis as they see fit, but no less than annually. Following each meeting, the IDMC will report their findings and recommendations to the TSC and to the TMG.

Interim analysis (split by treatment group) of IBDQ, modified CTCAE Version 4 grading, EORTC QLQ-C30 and 38, side-effects, tolerability and other endpoints for all randomised patients will be supplied in strict confidence by the trial statisticians to the IDMC together with any other analyses that the IDMC may request. The complete IDMC reports will remain confidential to the IDMC members and statisticians providing the report, however the Chief Investigator and Trial Co-ordinator will receive subsets of the report as seen fit by the IDMC (e.g. accrual, compliance and data completeness). Basic accrual data and safety reports, aggregated across the two treatment groups will be produced at appropriate periodic intervals and distributed to the TMG.

The main criterion for early stopping of the trial by IDMC will be that evidence from the trial or from other sources supplies a) proof beyond reasonable doubt that for all, or for some types of patient, one treatment regimen is clearly indicated or contra-indicated in terms of a net difference in therapeutic effect or b) evidence that might reasonably be expected to influence routine clinical practice. Criteria for the above will usually be a difference in CTCAE Version 4 significant at $p<0.001$.

No results will be made available to participants or the sponsor until the IDMC consider the results to be clinically and statistically informative. The IDMC may recommend continuation beyond the planned number of patients in the trial if it is felt that further information is required to address reliably the hypothesis in question.

7.8 End of study

The study end date is deemed to be the date of the last data capture.

7.9 Archiving

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, for example CRFs, patient consent forms. These will be maintained by the Trial Co-ordinator at The Royal Marsden in a way that will facilitate the management of the trial, audit and inspection. They will be retained for a sufficient period (at least 15 years) for possible audit and inspection by the regulatory authority. Documents will be securely stored and access will be restricted to authorised personnel. An archive log will be maintained to track archived documents.

7.10 Publishing policy

All publications and presentations relating to the trial will be authorised by the TMG. Authorship will be determined by the TMG and will include the Chief Investigator, Co-investigators, Collaborators, and Trial Statistician.

Authors will only present data separately to the total data available, with the permission of the TMG, and not less than 6 months after publication of the main results.

8 CONFIDENTIALITY AND LIABILITY

8.1 Risk assessment

Generic Risk Assessment for hazards to patients, study and organisation have been performed for the trial.

8.2 Liability/Indemnity/Insurance

This study is an investigator-led trial. Indemnity for The Royal Marsden is provided by the usual NHS indemnity arrangements.

8.3 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only their Trial ID will be recorded on subsequent Case Report Forms. Patient addresses will be requested for distribution of quality of life questionnaires.

The research team will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified, other than reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

Data Protection Act (DPA)

The trial team will comply with all aspects of the DPA 1998. Any requests from patients for access to data about them held by the Royal Marsden Trial Team should be directed to the Trial Coordinator in the first instance who will refer the request to the Data Protection Officer at The Royal Marsden.

8.4 Ethical Considerations

It is the responsibility of the Chief Investigator to obtain a favourable ethical opinion (REC approval) prior to recruitment of patients into the study.

It is the responsibility of the Chief Investigator or nominated representative to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Patients must be informed about their right to withdraw from the trial at any point. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet according to national guidelines.

It is the responsibility of the Chief Investigator to obtain signed informed consent from all patients prior to inclusion in the trial, as per the Trust SOP for Obtaining Informed Consent in Research.

8.5 Tissue sample storage

All retained tissue samples will be processed and stored securely in Prof Yarnold's Office, RM, Sutton (paraffin blocks) and BLB, ICR, Sutton (frozen samples). At the end of the trial, samples will remain stored in the same locations for future approved research if patients consent to this.

9 FINANCIAL MATTERS

The trial is investigator designed and led. It has received funding from the Malaysian Palm Oil Board, which is a Malaysian government agency. Tocovid SupraBio is provided free of charge by the Malaysian pharmaceutical manufacturer, Hovid Berhad.

10 APPENDICES

Appendix 1 Modified IBDQv2
Appendix 2 EORTC QLQ-C30 & CR29
Appendix 3 Gastrointestinal Symptom Rating Scale version 3.0, Feb 2014
Appendix 4 Modified CTCAE (subset of CTCAE Version 4)

Appendix 1 **Modified IBDQv2**

Trial Number:	**Date completed:**	**Baseline/ 3mth/ 6mth/ 9mth/ 12mth/ 15mth/ 18mth/ 24mth**

In the last two weeks please tell us how often you have had:

		More than ever before	Extremely frequently	Very frequently	Moderate increase in frequency	Some increase in frequency	Slight increase in frequency	Not at all / normal
1	had your bowel open?							
2	felt tired and worn out?							
3	felt frustrated, impatient or restless?							
4	been unable to do what you want because of your bowels?							
5	had loose bowel movements?							
6	worried about your energy levels?							
7	worried about having to have something done about your bowels?							
8	you had to cancel an engagement because of your bowels?							
9	been troubled by pain in your bottom?							
10	felt generally unwell?							
11	worried about not being able to find a lavatory?							
12	been prevented doing leisure or sports by your bowels?							
13	been troubled by cramps in your tummy or bottom?							
14	been waking at night or having difficulty sleeping?							
15	been depressed or discouraged?							

		More than ever before	Extremely frequently	Very frequently	Moderate increase in frequency	Some increase in frequency	Slight increase in frequency	Not at all / normal
16	not gone somewhere because there is no lavatory nearby?							
17	passed a large amount of gas							
18	worried about getting to the weight you would like							
19	worried about your illness							
20	been troubled by bloating							
21	been relaxed and free from tension							
22	had a problem with bleeding from your bottom?							
23	been embarrassed about your bowels?							
24	felt like you need to have your bowels open but nothing happens?							
25	felt tearful and upset?							
26	been troubled by accidental soiling?							
27	felt angry as a result of your bowel problems?							
28	felt limited in sexual activity because of your bowels?							
29	felt disgusted about your bowel problems?							
30	felt irritable?							
31	experienced a lack of understanding from others?							
32	felt satisfied, happy or pleased with your life?							

IBDQ-B Score……..

Appendix 2

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Trial Number: _____

Please fill in today's date (Day, Month, Year): _____ / _____ / _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

Trial Number: _____

Please fill in today's date (Day, Month, Year): _____ / _____ / _____

During the past week :	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had any problems with your sense of taste?	1	2	3	4

During the past week :	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
Answer these questions ONLY IF YOU HAVE A STOMA BAG, if not please continue below:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4

Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarassed because of your bowel movement?	1	2	3	4

During the past 4 weeks:

	Not at All	A Little	Quite a Bit	Very Much
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4

For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

Appendix 3 **Gastrointestinal Symptom Rating Scale**

RMH Patient Number: _____ Date: _____

1. Please rate your symptoms during the last month by placing a tick in the box that best describes each symptom

	Never	Occasional	Frequently affecting your life	Causes major changes in your life
Experienced change in smell	☐	☐	☐	☐
Experienced change in taste	☐	☐	☐	☐
Bad breath/halitosis	☐	☐	☐	☐
Difficulty swallowing liquids	☐	☐	☐	☐
Difficulty swallowing solids	☐	☐	☐	☐
Belching or burping	☐	☐	☐	☐
Heartburn or acid regurgitation	☐	☐	☐	☐
Feeling full after small amount of food	☐	☐	☐	☐
Reduced appetite	☐	☐	☐	☐
Hiccups	☐	☐	☐	☐
Nausea/feeling sick	☐	☐	☐	☐
Vomiting/being sick/retching	☐	☐	☐	☐
Abdominal cramps/trapped wind	☐	☐	☐	☐
Upper abdominal pain/discomfort	☐	☐	☐	☐
Lower abdominal pain/discomfort	☐	☐	☐	☐
Pain around your bottom	☐	☐	☐	☐
Abdominal bloating/distension	☐	☐	☐	☐
Excessive passing of wind from your bottom	☐	☐	☐	☐
Stomach/abdominal gurgling	☐	☐	☐	☐
Need to rush to open bowels	☐	☐	☐	☐
Feeling that you have not emptied your bowel properly	☐	☐	☐	☐

SE 36, GSRS version 3.0, Feb 2014 **Please turn over page**

RMH Patient Number: _____ Date: _____

	Never	Occasional	Frequently affecting your life	Causes major changes in your life
Leakage/ soiling or lack of control of the bowel	☐	☐	☐	☐
Mucus in the stool	☐	☐	☐	☐
Greasy or oily stool	☐	☐	☐	☐
Bleeding from your bottom	☐	☐	☐	☐
Itchiness around the bottom	☐	☐	☐	☐
Woken from sleep to have bowels open	☐	☐	☐	☐
Tiredness/lethargy	☐	☐	☐	☐
Problems with passing/controlling urine	☐	☐	☐	☐
Sexual concerns	☐	☐	☐	☐

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Please turn over page

RMH Patient Number: _____ Date: _____

2. Please indicate how you would score your quality of life at present on the scale below

0 1 2 3 4 5 6 7 8 9 10

Very low Perfect

3. How much do your bowel symptoms affect your quality of life?

0 1 2 3 4 5 6 7 8 9 10

Not at all All the time

4. Currently, how often do you open your bowels? (please tick as many boxes as required)

	What is the least often you have your bowels open?	What is the most you have your bowels open?
Less than once a week	☐	☐
Once every 4-7 days	☐	☐
Once every 2-4 days	☐	☐
Once a day	☐	☐
2-3 times a day	☐	☐
4-6 times a day	☐	☐
7 or more times a day	☐	☐

5. Please tick the box(es) which best describe(s) the stool you pass:

Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)	☐
Type 2	Sausage-shaped but lumpy	☐
Type 3	Like a sausage but with cracks on its surface	☐
Type 4	Like a sausage or snake, smooth and soft	☐
Type 5	Soft blobs with clear-cut edges (passed easily)	☐
Type 6	Fluffy pieces with ragged edges, a mushy stool	☐
Type 7	Watery, no solid pieces. **Entirely Liquid**	☐

Appendix 4 Modified Common Terminology Criteria for Adverse Events (CTCAE) (CTCAEv4)

Please record the grade of disorders in the right-hand column: if no symptoms, score 0.

	Gastrointestinal Disorders - Grade					
	Adverse Event	**1**	**2**	**3**	**4**	**Grade**
1	**Abdominal Pain**	Mild Pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	
	Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
2	**Bloating**	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	
	Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
3	**Constipation**	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	
	Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					
4	**Diarrhoea**	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	
	Definition: A disorder characterised by frequent and watery bowel movements.					
5	**Dyspepsia**	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	
	Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach,bloating, heartburn, nausea and vomiting.					

	Gastrointestinal Disorders - Grade					
	Adverse Event	**1**	**2**	**3**	**4**	**Grade**
6	**Dysphagia**	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	
	Definition: A disorder characterized by difficulty in swallowing.					
7	**Faecal Incontinence active = urge incontinence passive = leakage**	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	
	Definition: A disorder characterised by the inability to control the escape of stool from the rectum.					
8	**Flatulence**	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	
	Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
9	**Frequency**	Mild, intervention not indicated	Moderate symptoms, limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	
	Definition: A disorder characterised by the need to pass stool much more frequently than is normal.					
10	**Nausea**	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	
	Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					

	Gastrointestinal Disorders - Grade					
	Adverse Event	**1**	**2**	**3**	**4**	**Grade**
11	**Oral Pain**	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	
	Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.					
12	**Rectal bleeding**	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	
	Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus.					
13	**Rectal pain**	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	
	Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
14	**Tenesmus**	Mild, intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	
	Definition: The sensation of feeling the rectum is still not empty even after passing a stool.					
15	**Urgency**	Mild, intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	
	Definition: A disorder characterised by the desperate need to open the bowel.					

	Gastrointestinal Disorders - Grade					
	Adverse Event	**1**	**2**	**3**	**4**	**Grade**
16	**Vomiting** Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	
17	**Gastrointestinal disorders –** **Other, specify below :**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of existing hospitalisation indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	

ADL – activities of daily living Instrumental ADL refers to preparing meals, shopping etc Self care ADL refers to bathing, dressing, feeding self etc

Completed by: Name _____ **Signature** _____ **Date** _____

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