The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Nadir Testosterone within first year of ADT predicts for time to castrate resistant progression: A secondary analysis of the PR-7 intermittent vs continuous ADT trial.

Klotz, et al

DOI: 10.1200/JCO.2014.58.2973

The information provided may not reflect the complete protocol or any previous amendments or modifications. As described in the Information for Contributors (http://jco.ascopubs.org/site/ifc/protocol.xhtml) only specific elements of the most recent version of the protocol are requested by *JCO*. The protocol information is not intended to replace good clinical judgment in selecting appropriate therapy and in determining drug doses, schedules, and dose modifications. The treating physician or other health care provider is responsible for determining the best treatment for the patient. ASCO and *JCO* assume no responsibility for any injury or damage to persons or property arising out of the use of these protocol materials or due to any errors or omissions. Individuals seeking additional information about the protocol are encouraged to consult with the corresponding author directly.

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AMENDMENT #7: 2008-JUN-13

NATIONAL CANCER INSTITUTE OF CANADA
CLINICAL TRIALS GROUP (NCIC CTG)

SOUTHWEST ONCOLOGY GROUP (SWOG)
CANCER TRIALS SUPPORT UNIT (CTSU)
CANCER RESEARCH UK
CLINICAL TRIALS AND STATISTICS UNIT, INSTITUTE OF CANCER RESEARCH (ICR-CTSU)

A PHASE III RANDOMIZED TRIAL COMPARING INTERMITTENT VERSUS CONTINUOUS ANDROGEN SUPPRESSION FOR PATIENTS WITH PROSTATE-SPECIFIC-ANTIGEN PROGRESSION IN THE CLINICAL ABSENCE OF DISTANT METASTASES FOLLOWING RADIOTHERAPY FOR PROSTATE CANCER

NCIC CTG Protocol Number: PR.7
SWOG Protocol Number: JPR.7
CTSU Protocol Number: JPR.7
UK Protocol Name: The Intercontinental Trial

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CLINICAL TRIALS GROUP

SUPPORTED IN CANADA BY SANOFI-AVENTIS

*RTOG members will participate in this study
via the Cancer Trials Support Unit (CTSU)

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AMENDED: 99-JUN-04; 00-JUL-18; 02-FEB-25; AMENDMENT #7: 2008-JUN-13

TREATMENT SCHEMA

Patients with adenocarcinoma of the prostate who have completed radiotherapy to the prostatic area.

- more than 12 months between the last day of radiation treatment and randomization
- patient must have a rising PSA level (serum PSA is > 3 ng/ml (3 µg/L)) and higher than the lowest level recorded previously since the end of radiotherapy (i.e. higher than the post-radiotherapy nadir).
- no definite evidence of distant metastasis (radiological changes compatible with non malignant diseases are acceptable)
- hormonal therapy received in association with and either prior to, during, or immediately post radical radiotherapy or prostatectomy must have been received for a maximum duration of 12 months and completed at least 12 months prior to randomization.

Stratification

1. Prior radical prostatectomy: yes versus no
2. Time since completion of radiotherapy: > 1 to 3 years versus ≥ 3 years
3. Baseline PSA value: 3 ng/ml to 15 ng/ml versus > 15 ng/ml (3 to 15 µg/L versus > 15 µg/L)
4. Neo-adjuvant, concurrent, or adjuvant cytoreduction in association with the radical radiotherapy treatment or prostatectomy for a maximum duration of 12 months and completed at least 12 months prior to randomization: yes *versus* no (Patients with greater than 12 months of this treatment and/or treatment completed less than 12 months prior to randomization are not eligible.)

<table>
<tr><td rowspan="5">Patients with adenocarcinoma of the prostate who have PSA progression following radiotherapy</td><td rowspan="5">RANDOMIZATION</td><td colspan="3">ARM 1: IAS Arm (Intermittent Androgen Suppression)</td><td rowspan="5">Until Hormone Resistance</td></tr>
<tr><td>Initial Treatment Interval</td><td>Non-treatment Interval</td><td>Subsequent Treatment Interval</td></tr>
<tr><td>Antiandrogen* (min. 4 weeks)

LHRH agonist (x 8 months)</td><td><u>Start Non-treatment Interval</u> if <u>all</u> of the following criteria are met**:
• PSA < 4 ng/ml (4µg/L) AND < baseline PSA
• PSA not more than 1 ng/ml above last PSA
• No other evidence of clinical disease progression

Monitor PSA levels every 2 months***and continue on observation as long as:
• PSA remains < 10 ng/ml (10µg/L)
• there is no other evidence of disease</td><td><u>Resume IAS</u> when either:
• PSA > 10 ng/ml (10µg/L)
<u>or</u>
• Evidence of disease progression during an off treatment interval

Antiandrogen* (min. 4 weeks)

LHRH agonist (x 8 months)

Reassess for start of subsequent non-treatment intervals.</td></tr>
<tr><td colspan="3">ARM 2: CAD Arm (Continuous Androgen Deprivation)</td></tr>
<tr><td colspan="3">Antiandrogen* (min. 4 weeks)

LHRH agonist (or orchiectomy)</td></tr>
<tr><td colspan="5">Planned Sample Size: 1340 patients</td></tr>
</table>

* For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician. It is recommended patients off study restarting LHRH analog should also begin with a minimum of 4 weeks

** If ALL of the above criteria to begin a non-treatment interval have not been met, the patient should NOT start the off treatment interval and should receive continuous LHRH analog.

*** If the patient meets the criteria to restart androgen suppression at the first 2 month assessment, the patient should be restarted on continuous androgen suppression and should not be evaluated for further non-treatment intervals.

Primary and Secondary Endpoints

- Survival
- Time to hormone-resistance
- Quality of life

Other Endpoints

- Serum Cholesterol/HDL/LDL

IAS Arm Only:

- Duration of treatment and non-treatment interval
- Time to testosterone recovery
- Time to recovery of potency

NCIC CTG centres only:

- Translational Research: A prospective search for blood markers or predictive factors.

1.0 OBJECTIVES

1.1 To compare the survival (10.1) of patients randomized to intermittent androgen suppression (IAS) to that of patients randomized to continuous androgen deprivation (CAD) for patients with PSA evidence of progression in the clinical absence of distant metastases following previous radical radiotherapy treatment of prostate cancer.

1.2 To compare the time to the development of hormone-resistance (10.2) in patients randomized to intermittent androgen suppression (IAS) to that of patients randomized to continuous androgen deprivation (CAD) in this patient group.

1.3 To compare the effects of these treatments on measures of quality of life in this patient group, by using the EORTC QLQ-C30 and trial specific questionnaire.

1.4 To compare the serum cholesterol and HDL/LDL levels at 3 years with those at baseline, and to compare them annually between the patients randomized to intermittent androgen suppression (IAS) to that of patients randomized to continuous androgen deprivation (CAD) in this patient group.

1.5 Additional objectives on the Intermittent (IAS) Arm are to evaluate the duration of treatment and non-treatment intervals, the time to testosterone recovery (return to pre-therapy levels), and the time to recovery of potency.

1.6 In NCIC CTG centres, Putative Translational Research Prognostic Factors (See 2.6)

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Epidemiology Information of Prostate Cancer

Prostate cancer is the most common malignancy in North American men, with an estimated 244,000 new cases in the United States in 1995, and is the second leading cause of cancer deaths.[1] Prostate cancer incidence has increased 50% between 1980 and 1990.[2]

2.2 Treatment of Localized Disease

The two potentially curative modalities for localized disease are radical prostatectomy and radiation therapy. With standard radiotherapy, 30% of patients will still have positive biopsies at 2-3 years after treatment,[3] and twice as many will have biochemical evidence of recurrence (PSA), which may be either distant or local. [4]

2.3 Alternative Approaches to Patients who have Failed Radiation Therapy with Rising PSA

The treatment of patients who have been radiated for localized prostate cancer who have rising PSA is controversial. A number of treatment strategies are utilized in Canada.

The commonest strategy is initiation of androgen-ablative therapy. Usually this therapy is continuous but nowadays can be intermittent. The advantages are that a PSA response is seen in 95% of patients. The disadvantage is the substantial morbidity of long-term androgen ablation therapy and the lack of evidence supporting the benefit of early intervention. A study is currently ongoing in Europe comparing early to delayed intervention.[5] The results of this study are incomplete at present. The EORTC (European Organization for Research and Treatment of Cancer) has two studies addressing early versus delayed hormone therapy in progress - in previously untreated non-metastatic asymptomatic patients (EORTC 30891) and in those with elevated or rising PSA levels following definitive therapy (EORTC 30943).

A second approach is watchful waiting, with intervention with androgen ablation when the patient develops symptoms of advanced disease (usually metastatic). The benefits of this approach are reduced morbidity of treatment. The disadvantages relate to concerns that delayed treatment may result in shorter survival and an increased disease-related morbidity. A secondary issue is the patient's concern that he is not being treated while his PSA is rising.

A third approach is salvage radical prostatectomy. This has the advantage of attempting to convert radiation failure into a cure. The disadvantages are that the operation rarely eradicates all disease and the surgical morbidity following radiotherapy is high. Positive margins are reported in 80% of patients undergoing salvage prostatectomy. The rate of incontinence is 50%; impotence occurs in 90%. There is little enthusiasm for this modality in North America.

The fourth option is cryosurgical ablation of the prostate.[6] This is a new approach which is considered experimental. The data varies widely relative to the local response rate and to the surgical morbidity using cryosurgery following radiation. Recent reports suggest that the incontinence rate is 30 to 50%. This approach has potential, but is currently not widely utilized and awaits further confirmatory and comparative studies before being considered acceptable therapy.

Thus there is no "standard" therapy for this group of patients. The use of intermittent androgen ablation offers the potential for an improved quality of life during the non-treatment interval, decreased cost of therapy compared to continuous androgen ablation, and perhaps an improvement in overall survival. This remains to be determined by studies such as the one proposed herein.

2.4 PSA Threshold for Intervention

The Canadian practice pattern for management of locally or biochemically recurrent prostate cancer is very diverse. A recent survey of urologists (members of the Canadian Uro-oncology Group) and radiation oncologists (members of the Canadian Association of Radiation Oncologists with an interest in prostate cancer) revealed that 20% intervene when a rising PSA is still <10 ng/ml, 18% when it is > 10 ng/ml but < 20 ng/ml, 32% when the PSA is > 20 ng/ml but <50 ng/ml, and 24% when the PSA is > 50 ng/ml or when there are overt distant metastases. There is little data demonstrating that early intervention in such patients will improve survival or quality of life, although a recent publication by the Medical Research Council (MRC) for locally advanced or metastatic prostate cancer shows a survival advantage for early intervention versus delayed intervention.[5]

2.5 Rationale for Intermittent Treatment

Androgen deprivation of androgen sensitive tumour results in a high rate of apoptotic regression involving a number of androgen-repressed genes, resulting in a marked decrease in both differentiated cells and androgen-dependent tumorigenic stem cells. Progression to autonomy involves a 500 fold increase in androgen-independent stem cells [1,2,7] as a result of androgen deprivation.

Successive waves of apoptosis have been demonstrated in the non-malignant rat prostate after repeated withdrawal of testosterone stimulation, indicating that despite complete glandular involution, re-stimulation with testosterone not only induces regrowth but also restores androgen dependence.[8] Repeated responses to androgen deprivation have been demonstrated in the androgen dependent Shionogi mouse mammary carcinoma, with a mean time to androgen independence of 150 days as compared to 50 days for tumours not re-exposed to androgen after initial castration.[1] In LNCaP tumours, 4-5 cycles of intermittent androgen suppression were possible before progression developed, with a 3-fold prolongation of the time to androgen-independence.[9] The first report of the concept of intermittent therapy applied clinically in the pre-PSA era was published by Klotz, et al[10] in 1986. More recently, Goldenberg, et al[11] have reported a series of 52 men with either localized or metastatic prostate cancer (14 D2, 10 D1, 24 C, 2 B2, 2 A2) treated with intermittent androgen suppression. The mean time to progression was 35.5 months, with a return of general well-being, pretreatment potency and erectile function in the non-treatment intervals.

2.6 Translational Research: A Prospective Search For Blood Markers as Predictive Factors (For NCIC CTG centres only)

Phase II studies of intermittent hormonal therapy in prostate cancer have demonstrated that the time between cessation of one cycle and the time when it is necessary to start the next (the non-treatment interval) varies from 2 to 24 months. The choice between continuous and intermittent hormone therapy would be made more rational for the individual patient if those with a longer non-treatment interval, and hence more likely to benefit from the intermittent schedule, could be recognized in advance. One way of doing this would be to identify a marker in the blood that would reliably predict the non-treatment interval.

There are a number of potential candidates: CAG repeat length on the androgen receptor, ultrasensitive PSA, prostate specific membrane (PSM), prostate specific protein (PSP94), PSA mRNA, Insulin-like growth factor (IGF), and markers of oxidative stress.

This study will examine the CAG repeat length, IGF, oxidative stress markers and PSA mRNA. Samples of serum and DNA extracted from blood (see 9.0) will be collected and may be used for some of the above tests or other tests that may be developed in future. RT-PCR for PSA mRNA will be carried out only in Toronto due to the infeasibility of transporting frozen specimens.

A summary is provided of the hypotheses to be tested:

A. Insulin-like Growth Factors (IGFs)

There is evidence that prostate cancer cells proliferate in response to IGFs. The activity of the IGF mitogen system involves IGFBP-proteases liberating IGFs from IGF binding proteins (IGFBPs) and these IGFs reacting with cell receptors. In tissue, prostate specific antigen (PSA) behaves as an IGFBP-protease.

Hypotheses to be tested: At castrate levels of testosterone, there will be changes in IGF-1, IGF-2, IGFBPs -1,-2 and -3 and free IGF

IGF-1 levels before and during treatment are related to prognosis

B. Trinucleotide (CAG) repeat allele length of the androgen receptor

The number of CAG repeats in the androgen receptor varies between 9 and 30. This number is highest in Asians (who have a low incidence of prostate cancer) and lowest in African-Americans (who have a high incidence). The length of the trinucleotide repeat sequence inversely correlates with the risk of developing prostate cancer. A recent study suggests that there is an association between short trinucleotide repeat sequence and high grade histology, extraprostatic spread and distant metastases. Since the trinucleotide repeat sequence is stable even in hormone-resistant prostate cancer, it is thought that the CAG-repeat length in circulating leukocytes would be comparable to that in the individual's prostate cancer cells. It is also reasonable to speculate that the response of prostate cancer to androgen ablation is a function of the trinucleotide repeat sequence length.

Hypotheses to be tested: Trinucleotide repeat sequence of circulating blood cells predicts:

- for duration of response to androgen ablation and patient survival
- the duration of the individual non-treatment interval in IAS

C. Oxidative Stress

Thirty per cent of men in the fourth decade of life have microfocal prostate cancer. Factors (perhaps even androgens themselves) that are thought to accelerate microfocal to frank cancer have in common the element of oxidative damage to macromolecules, including membrane-based enzymes and DNA. Vitamin E, selenium and carotenoids are antioxidants that may slow this progression. Androgen deprivation may thus be expected to reduce oxidative stress. Thus levels indicative of oxidative stress (MDA, MDA-DNA adducts, protein oxidation and serum antioxidant levels) might:

- be related to progression-free survival in treated patients
- predict the duration of non-treatment intervals in patients on intermittent androgen suppression (IAS)

D. RT-PCR of circulating prostate cancer cells (Ontario (Toronto-Ottawa area) centres only)

RT polymerase chain reaction for PSA mRNA transcripts detects circulating prostate cancer cells at low levels in peripheral blood. Positivity predicts for biochemical failure after radical prostatectomy and for survival in cases of androgen-independent metastatic disease.

Hypotheses:RT-PCR positivity

- is a prognostic indicator for overall survival
- can define a sub-population more appropriately treated by IAS
- is a better marker of tumour activity than PSA and thus may help determine an optimum non-treatment interval in IAS

2.7 Quality of Life

2.7.1 *Rationale for QOL collection*

Patients who have a relapse of their cancer after they had hoped it was cured by radical radiotherapy face a major shock of the incurable status. How they cope and adjust to this is poorly documented in the QOL research. In addition they face choices and the instigation of new therapies which whilst improving the PSA value actually frequently introduce risks and side effects. Hormonal therapy interferes with energy level, mood and sexual function for example which in turn affect role function, and relationships. This is not well studied. Whilst it is hoped that intermittent therapy may offer QOL advantages it may also produce more anxiety or disappointment. Recovery of QOL in the non-treatment time is not fully known. A pilot study (personal communication, Graeme Duncan) of QOL in this setting also revealed an unexpected complaint of more nocturia in patients on treatment. Finally, if the primary study endpoints are indeed equivalent then the QOL aspects become central to clinical decision making and knowing how best to advise patients.

The frequency of quality of life follow-up in the study arises because of the variable nature of the intermittent arm. The problem is capturing data both on- and non-treatment. Since the non-treatment intervals will vary, patients on the intermittent arm quickly become unsynchronized. On the other hand, it is essential in comparing the QOL data that we evaluate QOL at the same points in time in both arms of the study. Thus we must assess QOL frequently enough, especially in the earlier part of the trial.

2.7.2 *Formulation of the PR.7 trial specific questionnaire*

The EORTC core QOL questionnaire (QLQ-C30) will be used, together with a trial specific checklist. This checklist was developed in conjunction with members of the trial committee, QOL chair, SWOG and others. The NCIC CTG QOL data bank and items currently in use in other trials were reviewed. A literature review of themes in this context was under taken.[14,15,16] The resultant checklist is comprised of items (with modification) from other NCIC CTG prostate studies (PR.3 and PR.5) as well as other studies that assess sexuality (EN.5).

In addition modified items derived from the Illness Distress Scale,17 the McGill Quality of Life Questionnaire [18,19] and FACT-G [20] have been incorporated. In particular in this context of hormonal treatment for relapsed incurable prostate cancer the themes of sexuality, family and caregiver relationships and existential aspects of suffering are explored.

2.8 Baseline Assessment of Patients' Nutrition

There is a high correlation between (r=0.62) fat intake of various populations and their risk for prostate cancer mortality. For example, the United States and Japan have similar standards of vital statistics and health care facilities; but a nine-fold difference in prostate cancer (CAP) mortality. The intake of dietary fat in Japan in 1955 was 10% of total calories. Genetic differences between Americans and Japanese are an unlikely explanation for the discordance of CAP mortality as Japanese immigrants to the United States experience a rise in prostate cancer risk. This risk is intermediate between host nation and original nation and achieves that of the host nation in second generation immigrants. The increase risk in immigrants from low to high risk areas occurs within 12 years, adding further credence to the concept of late-stage environmental effects on disease progression. Nutritional changes such as increasing dietary fat may be responsible for these rate changes. Aside from the observational data, a review of hypothesis testing in the epidemiologic literature also demonstrates that the association between dietary fat consumption and CAP is consistent. Eleven of 14 and 4 of 5 case-control and cohort studies, respectively, have confirmed the association.

In the murine model, a high fat, linoleic acid rich diet enhanced the growth of LNCAP prostate cancer cells in male nude mice. These results have also indicated that changing dietary fat consumption from high (40.9%) to low (21.3%) once LNCAP xenografts are established can slow tumour progression.

Dietary fat consumption may contribute to prostatic carcinogenesis via oxidative lipid peroxidation. Lipid peroxides and their products can cause damage to membrane bound enzymes and other macromolecules, including DNA. Malondialdehyde (MDA) results from the oxidation of polyunsaturated fatty acids (PUFA) in biological membrances, and is considered a major mutagenic and carcinogenic product of lipid peroxidation. MDA also has the capacity to generate other reactive oxygen species and lipid hydroperoxides. MDA-DNA adducts have been proposed as markers of DNA damage resulting from endogenous oxidative processes.

Thus the study will determine if dietary factors (dietary fat consumption as a percentage of total calories) at baseline are associated with time to disease progression. These data will also be important for covariate adjustment in determining the significance of oxidative biomarkers, which are being evaluated in the translational companion study.

3.0 BACKGROUND THERAPEUTIC INFORMATION

During the course of this study, patients may be treated with any commercially available LHRH analog and antiandrogen. Appendix IX provides a list of all agents commercially available at the time, their doses and schedule.

For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare at each on-treatment interval. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician. If antiandrogen is stopped after the initial 4 weeks it may be restarted at the investigator's discretion any time during the LHRH agonist treatment interval. Patients may switch between drugs at any time during protocol treatment.

3.1 LHRH Agonists

Short-term worsening of signs and symptoms associated with prostate cancer, such as increased bone pain or urinary obstruction, have been reported at the initiation of therapy. This is unlikely after prior anti-androgen treatment. This could contribute in some patients (e.g. those with metastatic vertebral lesions or a history of urinary obstruction) to paralysis or renal failure with or without fatal complications. Therefore it is recommended that patients are treated with an oral anti-androgen for at least 4 weeks beforehand to counter any "flare" phenomenon. The patient may or may not then continue the anti-androgen at the physician's discretion.

3.1.1 *Buserelin (Suprefact Depot®)*

Buserelin acetate is a synthetic peptide analog of natural gonadotrophin releasing hormone. Chronic administration results in the inhibition of gonadotrophin production, thus inhibiting steroid hormone production from the testis. There is a transient increase in testicular steroids at the commencement of treatment. Intramuscular injection of the depot preparation prolongs plasma levels of leuprolide for a month. Decreased testicular size, hot flushes, impotence, gynecomastia and a decrease in libido are all related to hormonal changes consequent to the primary effect of the agent. The reversibility of the clinical symptoms of hypogonadism that occur has not been established. Other serious adverse effects that have been reported are: congestive cardiac failure, EKG changes, hypertension and hypotension, myocardial ischemia and infarction, thrombosis, pulmonary embolism and strokes. The drug literature lists a large number of other associations.

Buserelin (as Suprefact depot 2 month) is given subcutaneously every 2 months into the skin of the lateral abdominal wall. It is supplied as a sterile ready to use syringe for subcutaneous use, the needle containing 6.3 mg (for the 2 month buserelin base) in two D, L lactide-co-lactide rods. Likewise, buserelin may also be given subcutaneously every 3 months at a dose of 9.45 mg (as Suprefact Depot 3 month). Protect from light, moisture and heat.

Store intact package between 15^{o}C and 30^{o}C.

3.1.2 *Goserelin (Zoladex®)*

Goserelin is a synthetic decapeptide analog of gonadotrophin releasing hormone. Administered chronically, it inhibits gonadotrophin production thus resulting in testicular regression. The serum testosterone falls to the levels seen in surgically castrated men within three weeks and is maintained at these levels as long as therapy is continued. Patients frequently (> 50%) experience hot flushes, decreased libido and erections, and less frequently, (< 10%), gynecomastia and local pain at the injection site. Rarely (< 1%) cardiovascular or cerebrovascular accidents, skin rashes and hematological complications have been noted.

Goserelin depot is released continuously over at least 28 days (Zoladex) or 3 months (Zoldex LS) from a cylindrical rod of biodegradable copolymer. It is supplied as a sterile, ready-to-use syringe for subcutaneous use, the needle containing 10.8 of goserelin in the D-L Lactide-glycolide copolymer rod. The rod is implanted into the subcutaneous tissue of the anterior abdominal wall following the recommended procedure. Protect from light and moisture. Store in intact package between 2ºC and 25ºC.

UK CENTRES: If the patient draws the Intermittent Androgen Suppression (IAS) arm they must receive the monthly preparation. If the patient draws the Continuous Androgen Deprivation (CAD) arm of the study the injection can be given either monthly or every three months. Patients must not receive the three monthly preparation if on the IAS arm.

3.1.3 *Leuprolide*

Leuprolide is a synthetic nonapeptide analog of gonadotrophin releasing hormone. Chronic administration results in inhibition of gonadotrophin production, thus inhibiting steroid hormone production from the testis. There is a transient increase in testicular steroids at the commencement of treatment. Intramuscular injection of the depot preparation prolongs plasma levels of leuprolide for a month.

Decreased testicular size, hot flushes, impotence, gynecomastia and a decrease in libido are all related to hormonal changes consequent to the primary effect of the agent. The reversibility of the clinical symptoms of hypogonadism that occur has not been established. Other serious adverse effects that have been reported are: congestive cardiac failure, EKG changes, hypertension and hypotension, myocardial ischemia and infarction, thrombosis, pulmonary embolism and strokes. The drug literature lists a large number of other associations. Leuprolide is available in two depot formulations, one given subcutaneously (Eligard) and the other given intramuscularly (Lupron Depot).

3.1.3.1 *Leuprolide (Eligard®)*

Eligard is given subcutaneously every 1 month (Eligard 75 mg 1 month Depot), 3 months (Eligard 22.5 mg 3 month Depot), 4 months (Eligard 30 mg 4 month Depot) or 6 months (Eligard 45 mg 6 month Depot). Eligard 22.5 mg (3-Month) is supplied in two separate prefilled, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. One syringe contains the ATRIGEL® Delivery System, and the other contains leuprolide acetate. The ATRIGEL® Delivery System is a polymeric (non gelatin containing) delivery system consisting of a biodegradable, 45% poly (DL-Lactide-co-glycolide)(PLG) polymer formulation dissolved in a biocompatible solvent, 55% N-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains 28.2 mg lyophylized leuprolide acetate and is designed to deliver 22.5mg of leuprolide acetate at the time of SC injection. Eligard 22.5 mg (3-Month) is available in a single use pouch packaging. The pouch packaging contains two-syringe mixing system, a 20-gauge half-inch needle, and a silicone desiccant pouch to control moisture uptake.

3.1.3.2 *Leuprolide (Lupron Depot®)*

Lupron Depot is given intramuscularly every 28 days (Lupron Depot 1 month) or every 3 (Lupron 3 month) or 4 months (Lupron Depot 4 month). The injection site should be varied periodically. Each single dose vial of Lupron Depot 3 month contains 22.5 mg incorporated as sterile biodegradeable lyophilized microspheres, purified gelatin polyactic/polyglycolic acid and D-mannitol. The accompanying ampoule of diluent contains carboxymethylcellulose sodium 5 mg, D-mannitol 50 mg, 1 mg polysorbate 80 and water for injection. Reconstitute each vial with 1 ml of the special diluent. Discard the remaining, unused diluent.

3.1.3.2 *Leuprolide (Leuprorelin, Prostap)*

UK CENTRES: Leuprorelin (Prostap) is supplied in a 3.75 mg (via intramuscular or subcutaneous injection every month) or a 11.25 mg (via subcutaneous injection every 3 months). It is given every month if the patient draws the Intermittent Androgen Suppression (IAS) arm. If the patient draws the Continuous Androgen Deprivation (CAD) arm of the study the injection can be given either monthly or every three months. Patients must not receive the three monthly preparation if on the IAS arm. The injection site should be varied periodically. Each single monthly dose vial contains 3.75 mg of leuprorelin acetate incorporated as sterile biodegradable lyophilized microspheres, purified gelatin polyactic/polyglycolic acid and D-mannitol. The accompanying ampule of dilutent contains carboxymethylcellulose sodium 5 mg, D-mannitol 50 mg, 1 mg polysorbate 80 and water for injection.

3.2 Antiandrogens

3.2.1 *Nilutamide*

Nilutamide is contraindicated in patients with severe hepatic impairment, in patients with severe respiratory insufficiency, and in patients with hypersensitivity to nilutamide or any component of this preparation.

Since nilutamide has an effect on certain hepatic microsomal enzymes, it will reduce the metabolism of certain drugs such as warfarin-type anticoagulants, phenytoin, chlordiazepoxide, lidocaine, diazepam and theophylline. Blood levels of these drugs may increase and dose adjustments be required. Patients should be warned against alcohol consumption because of possible disulfiram like reaction.

An increase in visual adaptation time when passing from light to darkness is one of the most frequently reported adverse effects. This can decrease, even with continued treatment, and can be ameliorated with the use of sunglasses. Patients must take care when driving or operating machinery. Other visual disturbances seen are impaired vision of colours and, rarely, blurred vision, photophobia and dazzling.

Complaints of hot flushes, decreased libido and impotence are frequent but these reports have been in conjunction with castration.

Nausea, vomiting, constipation, rarely diarrhea and gastric pain have been reported.

Rare cases of hepatic dysfunction have been reported. Interstitial pneumonitis has been reported in 2% of patients exposed to nilutamide in controlled clinical trials.[21] As well, tachycardia, hypertension and rashes have occurred rarely.

Nilutamide (Anandron), should be administered at 300 mg daily for one month and then reduced to 150 mg daily for patients continuing antiandrogen after the flare period. It is commercially available in Canada in 50 mg tablets. Store at room temperature.

3.2.2 *Flutamide*

Flutamide is a potent inhibitor of androgen uptake in endocrine-target tissues. Its major metabolite is the alpha hydroxylated derivative and both compounds have a plasma half-life of 5 to 6 hours. Twenty-eight percent of the drug is excreted in the urine within 24 hours.

By elevating the plasma testosterone and estradiol levels, flutamide can cause fluid retention but the major toxicity, which has been fatal, is hepatic failure. The development of pruritus, dark urine (the urine can be coloured amber or yellow-green anyway from the drug), jaundice or ALT $\geq$ 2x upper normal limit is an indication that the drug should be discontinued. Periodic liver function tests as a routine are recommended. The hepatic damage is usually reversible.
Gynecomastia and/or breast tenderness, sometimes with galactorrhea, can develop. These usually disappear upon discontinuation or a reduction in dosage. (These symptoms do not disappear while continuing treatment.)

Flutamide can cause nausea, vomiting, an increase in appetite, diarrhea or rarely, anorexia and constipation.

Also rare are thrombophlebitis, pulmonary embolism and myocardial infarction. Insomnia and lassitude are more common than headache, blurred vision and decreased libido which occur rarely. Flutamide is available as 250 mg yellow tablets (Euflex, Canada; Drogenil, UK) and 125 mg capsules (Eulexin, USA). Store at room temperature.

3.2.3 *Bicalutamide*

Bicalutamide is a potent nonsteroid antiandrogen without androgenic or progestational properties. The chemical name is Propanamide, N-[4-cyano-3-(trifluoromethyl)-phenyl]-3-[(4-fluorophenyl) sulphonyl]-2-hydroxy-2-methyl-, (+/-). It is a racemic mixture, the antiandrogen activity residing exclusively with the (-) or (R) (active) enantiomer.

Gynecomastia with breast tenderness, hot flashes and pruritis are the most frequent adverse effects of the drug. Other toxicity directly related to the pharmacological effect of the drug is infrequent. Asthenia, pelvic pain, peripheral edema, diarrhea, rash, constipation, impotence, dyspnea, nausea and pain have all been recorded. No change in cardiac status during long-term administration of bicalutamide with at least 50 mg daily has been observed. Since transaminase abnormalities and rarely jaundice have been reported with the use of bicalutamide, periodic liver function tests should be considered. Abnormalities are usually reversible upon discontinuation of drug. In bicalutamide monotherapy at 150 mg daily only 2.9% of subjects were withdrawn because of treatment related toxicity (although 5.2% were withdrawn in total). The principal adverse events were gynecomastia (26%), breast pain (32%) and hot flashes (9.2%) although about 2% experienced nausea, diarrhea and/or constipation. Changes in liver function are infrequent (< 2%) and have resolved despite continuing therapy, although in a few cases, jaundice has occurred for which bicalutamide-induced hepatotoxicity cannot be excluded.

Bicalutamide (Casodex) is a white tablet containing 50 mg. Taken 50 mg PS as a once daily dose. Store at room temperature in a dry place.

3.2.4 *Cyproterone Acetate (UK Centres)*

Cyproterone acetate is a steroid with dual properties. It is an antiandrogen that blocks the binding of dihydrotestosterone, the active metabolite of testosterone, to the specific receptors in prostatic carcinoma cells. It is also an antigonadotrophic agent that inhibits secretion of luteinising hormone and subsequent diminishes production of testosterone.

Cyproterone acetate is contraindicated for hepatic disease, Dubin-Johnson syndrome, Rotor syndrome, severe diabetes, sickle-cell anaemia, previous or existing thromboembolic disorders, renal insufficiency, and severe chronic depression.

Direct hepatic toxicity, including jaundice, hepatitis, and hepatic failure, has been reported in patients treated with cyproterone acetate 200 to 300 mg daily, usually after several months of treatment. In view of the hepatic toxicity, where fatal cases have been observed, cyproterone acetate should be restricted to short-term use to block tumour flare associated with LHRH analog therapy, hot flushes after orchidectomy or LHRH analog therapy, and for patients who have not responded to other treatments.

Inhibition of spermatogenesis (production of abnormal spermatozoa, impotence, reversible infertility) and gynaecomastia (breast enlargement, breast tenderness, galactorrhoea, benign nodular hyperplasia of the breast) are the most frequent adverse effects due to the hormonal effects of the drug. These reactions usually subside after discontinuation of treatment or a reduction in dosage.

Impairment of carbohydrate metabolism, anemia, thrombocytopenia, and suppression of adrenocortical function have been reported. For safety reasons liver function tests, fasting blood glucose assessment, glucose tolerance tests, hematological assessment, and adrenocortical function tests are recommended before and during therapy.

Cardiovascular diseases (hypotension, hemorrhage, cardiovascular disorder, thrombosis), respiratory diseases (shortness of breath, asthma), gastrointestinal diseases (constipation, diarrhea, indigestion, anorexia, nausea, vomiting), and rarely osteoporosis have been reported.

Cyproterone acetate may alter metabolism (leading to fluid retention, hypercalcemia, and changes in plasma lipid profile), reduce sebum production (leading to dryness of skin and transient patch loss of body hair), and cause fatigue, lassitude, asthenia, hot flashes, increased sweating, abnormality of accommodation, abnormal vision, blindness, as well as depression. It is advised that marked lassitude and asthenia necessitate special care when driving or operating machinery. In addition, patients should be warned against alcohol consumption during cyproterone therapy.

Cyproterone acetate (Cyprostat) is available as 100 mg white tablets. It is administered 300 mg daily in 3 divided doses and taken after meals.

4.0 TRIAL DESIGN

A randomized comparison of intermittent androgen suppression (IAS) with continuous androgen deprivation (CAD) in patients with PSA-evidence of progression in the absence of distant metastases following previous radical radiotherapy treatment of prostatic cancer. (See 5.0)

4.1 Stratification

1. Prior radical prostatectomy: yes versus no
2. Time since completion of the radical radiotherapy: 1-3 years versus $\geq$ 3 years
3. Baseline PSA value: 3 ng/ml to 15 ng/ml versus > 15 ng/ml (3 µg/L to 15 µg/L versus > 15 µg/L)
4. Neo-adjuvant, concurrent, or adjuvant cytoreduction in association with the radical radiotherapy treatment or prostatectomy for a maximum duration of 12 months and completed at least 12 months prior to randomization: yes versus no (Patients with greater than 12 months of this treatment and/or treatment completed less than 12 months prior to randomization are not eligible.)

4.2 Randomization

Patients will be randomized to one of the following two arms:		
IAS Arm	LHRH analog + non-steroidal antiandrogen*	8 months then if PSA < 4 ng/ml (4µg/L), observe until criteria of progression (see 8.1.1) are met then restart. Intermittent hormone therapy continues until hormone resistance (10.3) criteria are met.
CAD Arm	LHRH analog + non-steroidal antiandrogen* OR bilateral orchiectomy +/- non-steroidal antiandrogen*. The use of antiandrogen is optional where bilateral orchiectomy is performed.	Continuous until hormone-resistance (10.3) criteria are met.
* For safety reasons the antiandrogen must be given for minimum of 4 weeks to block tumour flare. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician. For detailed schedule see 8.1		

Planned sample size 1340 patients.

4.3 Inclusion of Women and Minorities

It is not relevant to consider gender in the design of this trial.

In prostate cancer, although black men have a poorer survival they also present with more advanced disease and previous studies have failed to show any interaction between race and the effect of treatment.[22] In particular, as far as hormone treatment is concerned, there seems to be no significant interaction between the effect of androgen blockade and survival.[23] Using a multivariate model, an adjusted retrospective comparison from the Walter Reed Hospital showed a strong tendency for black men to have a poorer recurrence-free outcome following radical prostatectomy for localized cancer and the authors suggest that the disease might be more aggressive in these patients.[24] However, this has not been established as fact and the previously-mentioned failure to demonstrate an interaction between treatment and race is of more relevance in relation to a study of hormonal manipulation in patients in whom local measures have already failed.

Insufficient ethnic data have been collected in NCIC CTG trials to be able to predict how many black men will be recruited to this study. SWOG has recruited about 20% in other studies and so it might be estimated that at least 10% of the patients will be black. For the reasons given above, however, no special sample size goal for black men is planned. Retrospective subset analyses by race may be performed in this study, but it is realized that the power of such comparisons will be low.

SWOG participates in the Minority Based CCOP and CTEP Minorities programs.

5.0 STUDY POPULATION

Patients with adenocarcinoma of the prostate who have completed radiotherapy to the prostatic area.

- more than 12 months between the last day of radiation treatment and randomization
- patient must have a rising PSA level (serum PSA > 3 ng/ml (3 μg/L)) and higher than the lowest level recorded previously since the end of radiotherapy (i.e. higher than the post-radiotherapy nadir).
- no definite evidence of distant metastasis (radiological changes compatible with non malignant diseases are acceptable)
- hormonal therapy received in association with and either prior to, during, or immediately post radical radiotherapy or prostatectomy must have been received for a maximum duration of 12 months and completed at least 12 months prior to randomization.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to assure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Histologically or cytologically confirmed adenocarcinoma of the prostate prior to the initiation of radiotherapy.

5.1.2 Previous pelvic radiotherapy for prostate cancer, either post radical prostatectomy or as primary management. Patients treated with brachytherapy with curative intent as the primary form of radiotherapy are eligible provided that the date of implant is > 30 months prior to randomization.

5.1.3 Serum PSA > 3 ng/ml (3 μg/L) and higher than the lowest level recorded previously since the end of radiotherapy (i.e. higher than the post-radiotherapy nadir) and must be done within one month (28 days) prior to randomization.

5.1.4 Serum testosterone > 5 nmol/L (145 ng/dl) and must be done within one month (28 days) prior to randomization.

5.1.5 No definite evidence of metastatic disease. (Patients with radiological findings strongly suggesting metastatic disease must not be entered into the study, but patients with radiological changes compatible with non-malignant diseases are acceptable.) Patients may have clinical evidence of local disease.

5.1.6 Chest x-ray has been performed within 8 weeks (56 days) prior to randomization and is negative for metastases. Bone scan has been performed within 8 weeks (56 days) prior to randomization and is negative for metastases.

5.1.7 No radiotherapy in the 12 months preceding randomization.

5.1.8 Hormonal therapy received in association with and either prior to, during, or immediately post radical radiotherapy or prostatectomy must have been received for a maximum duration of 12 months and completed at least 12 months prior to randomization.

5.1.9 ECOG performance status must be 0 or 1. (see appendix II)

5.1.10 Patient's age $\geq$ 16 years for Canadian and US centres, $\geq$ 18 years for UK centres. (Note that the lower age limit at each centre will be determined by that centre's policy regarding the age at which an individual may sign their own consent).

5.1.11 Patient's life expectancy is > 5 years.

5.1.12 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French. The baseline assessment must already have been completed. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible.

5.1.13 Laboratory requirements have been done within one month (28 days) prior to randomization:

- Bilirubin $\leq$ 1.5 x upper normal limit
- AST (SGOT) $\leq$ 1.5 x upper normal limit
- ALT (SGPT) $\leq$ 1.5 x upper normal limit
- LDH $\leq$ 1.5 x upper normal limit
- Creatinine $\leq$ 1.5 x upper normal limit

5.1.14 As it is unknown/uncertain whether these treatments may effect an unborn child, adequate birth control measures should be used by the participant or his sexual partner(s) (if of reproductive potential) while participating on this study.

5.1.15 Patient consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the NCIC CTG Clinical Trials Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is given in section 18.0. A copy of the initial REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to randomization or registration. Please note that the consent form for this study must contain a statement which gives permission for the NCIC CTG and monitoring agencies to review patient records (see section 18.0 for further details).

Southwest Oncology Group institutions will follow standard procedures for IRB approval and consent documentation.

5.1.16 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, toxicity, and follow-up. Patients may receive protocol treatment outside of the participating centre. If patients are treated outside the participating centre they must return to the participating centre at least once every four months to ensure protocol compliance and complete documentation of treatment and toxicity.

5.1.17 In accordance with NCIC CTG policy, LHRH analog and antiandrogen must begin within 5 working days of patient randomization. Patients for whom orchiectomy is planned may be given LHRH analog while awaiting surgery. Patients receiving LHRH analog may begin antiandrogen either prior to or simultaneously with LHRH analog administration to prevent flare response. Treatment should not commence until after randomization.

5.2 Ineligibility Criteria

Patients with any one of the following criteria are not eligible for admission to the study:

5.2.1 History of other malignancy within the last 5 years, other than treated basal or squamous carcinoma of the skin or superficial bladder cancer.

5.2.2 Chronic liver disease.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	History Physical Examination Rectal Examination Performance Status Weight	Within 2 weeks (14 days) before randomization
Hematology	Hemoglobin WBC and differential Platelet count	Within 1 month (28 days) before randomization
Biochemistry	Serum bilirubin Serum AST (SGOT) and ALT (SGPT) Serum LDH Serum creatinine Serum alkaline phosphatase Fasting Serum cholesterol/HDL/LDL PSA (Lowest previous PSA value since radiotherapy also required) Serum testosterone	Within 1 month (28 days) before randomization
Radiology	Chest x-ray	Within 8 weeks (56 days) before randomization
	Bone scan	Within 8 weeks (56 days) before randomization
Toxicity*	Baseline toxicity evaluation (to document residual toxicity from previous therapy and baseline symptoms)	Within 2 weeks (14 days) before randomization
Quality of Life	EORTC QLQ-C30 and trial specific questionnaire	
Other Investigations	Blood sample (see 13.1) (NCIC CTG Centres Only) Additional Blood Sample for RT-PCR testing (see 13.1) (Toronto centres only) Nutrition Survey (NCIC CTG centres only)	Prior to initiation of androgen ablation
* Toxicities will be recorded and graded according to the Common Toxicity Criteria Version 2.0 (Appendix V).		

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

7.1.1 *NCIC CTG Institutions*:

All eligible patients enrolled on the study by a participating treatment centre will be entered into a patient registration log provided by the NCIC CTG. This will automatically provide a serial number for that patient which should be used on all documentation and correspondence with the NCIC CTG.

All randomizations will be done centrally by the NCIC CTG and will be obtained by calling the NCIC CTG Clinical Trials Assistant at (613) 533-6430 or by faxing the eligibility checklist to (613) 533-2941 or (613) 533-2814. At the time of randomization, a copy of the completed eligibility checklist must be available.

The following information will be required:

- trial code (NCIC CTG PR.7)
- treatment centre and investigator
- date of REB (IRB) approval for study at participating centre
- patient's initials, hospital number and NCIC CTG serial number
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- completed eligibility checklist
- stratification parameters

7.1.2 *SWOG Institutions*:

Investigators will call the Southwest Oncology Group (SWOG) Data Operations Center in Seattle at 206/652-2267 between the hours of 6:30 a.m. and 1:30 p.m. (PT) Monday through Friday, excluding holidays. The SWOG Data Operations Center will confirm the patient is eligible per the current version of the eligibility checklist. In addition, the SWOG Data Operations Center will request the date informed consent was obtained and the date of Institutional Review Board (IRB) approval for each entry. The SWOG Data Operations Center will then contact the NCIC - Clinical Trials Group (NCIC CTG) to register and randomize the patient after which the SWOG Data Operations Center will contact the institution to confirm registration. SWOG members should not contact the NCIC CTG directly to enroll a patient. The NCIC CTG will forward a confirmation of treatment assignment to the SWOG Data Operations Center for routing to the SWOG participating institution. Please note: SWOG institutions will follow their normal procedures for documentation of IRB approval. Institutions must be prepared to give the stratification factors listed in 7.2 at the time of registration.

7.1.3 *CTSU Investigators*:

Prior to the recruitment of a patient for this study, investigators and their institutions must be registered members of the CTSU. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol. Patients can be registered only after all pertinent documents are approved and on file and eligibility criteria are met.

CTSU Procedures for Patient Enrollment: Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Note that the baseline Quality of Life Questionnaire must be completed by the patient within 2 weeks prior to randomization, but is submitted along with The Initial Evaluation form due 10 weeks after randomization. To enroll the patient, the investigator should complete the following forms:

- CTSU Patient Enrollment Transmittal
- Eligibility Checklist:

  Prior to randomizing patient, CTSU investigators should complete the form with exception of "NCIC CTG Patient Serial No.", "Intergroup Patient Serial No.", and the Randomization section. Fax form to CTSU Patient Registrar along with CTSU Patient Enrollment Transmittal. Hold onto Original form. (Within 10 weeks of randomization complete remaining sections of original Eligibility Checklist and mail to CTSU Data Center along with Initial Evaluation [pages 4-7 of Form 1].)

Registration forms should be faxed to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 pm Eastern time. The CTSU registrar will check the investigator and site information provided to insure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies.

Once investigator and patient eligibility are confirmed, the CTSU will contact the NCIC CTG to obtain a randomization assignment and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU will then contact the enrolling site and convey the patient ID number and the patient's treatment assignment. This will be confirmed by an e-mail or fax to the enrolling site.

7.1.4 UK Investigators:

This trial has received Multi-Centre Research Ethics Committee (MREC) approval. However, additional approvals must be obtained by each UK centre before randomizing patients into the trial:

- Each UK centre must obtain Local Research Ethics Committee (LREC) approval.
- Since this trial involves collaboration with a United States funding body, UK investigators require an approval from the Office for Human Research Protections (OHRP) in the United States Department of Health and Human Services (DHHS) (http://ohrp.osophs.dhhs.gov/). Hence, each UK centre must obtain its own Federal Wide Assurance (FWA) or Co-operative Project Assurance (CPA).
- Each UK centre must obtain an Administration of Radioactive Substances Advisory Committee (ARSAC) licence at the National Radiological Protection Board to approve the additional exposure to radioactive material or radiation.

Confirmation of LREC and FWA/CPA approval, as well as attainment of the ARSAC licence will be forwarded from each centre to the Clinical Trials and Statistics Unit of the Institute of Cancer Research (ICR-CTSU). The ICR-CTSU will then notify the approval of all pertinent documents to the NCIC CTG.

Once patient eligibility has been confirmed and informed consent form has been received, the clinician should contact the ICR to randomize the patient. All randomizations will be undertaken by the ICR-CTSU on behalf of the NCIC CTG. Randomizations will be obtained by calling ICR-CTSU at 020 8643 7150 or by faxing the eligibility checklist to 020 8722 4368 (Monday – Friday, 09h00 – 17h00, every working day). At the time of randomization, the following information will be required:

- Trial name (The Intercontinental Trial)
- Treatment centre and investigator
- Patient's initials, hospital number and date of birth
- Confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values
- Stratification parameters
- Confirmation of completed eligibility checklist (CRF-Form 1) and patient's written informed consent form

Eligibility will be confirmed via an eligibility checklist prior to release of a trial number and treatment allocation.

Randomization will be performed by computer-generated random permuted blocks within the stratification parameters. The ICR-CTSU will generate UK randomization lists (using the same stratification factors as at the NCIC CTG).

Randomization details, including trial number, treatment allocation, centre, and date of randomization will be emailed to the NCIC CTG on a regular basis (at least monthly or more frequently as accrual increases).

7.2 Stratification

1. Prior radical prostatectomy: yes versus no
2. Time since completion of the radical radiotherapy: > 1 to 3 years versus $\geq$ 3 years
3. Baseline PSA value: 3 ng/ml to 15 ng/ml versus > 15 ng/ml (3 µg/L to 15 µg/L versus > 15 µg/L)
4. Neo-adjuvant, concurrent, or adjuvant cytoreduction in association with the radical radiotherapy treatment or prostatectomy for a maximum duration of 12 months and completed at least 12 months prior to randomization: yes versus no (Patients with greater than 12 months of this treatment and/or treatment completed less than 12 months prior to randomization are not eligible.)

7.3 Randomization

Randomization will be given by telephone and confirmed by e-mail, fax or regular mail.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, except on disclosure of initial ineligibility.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death. The follow-up requirement for ineligible patients is minimal follow-up using a Form 5M.

AMENDED: 99-JUN-04; 00-JUL-18; 01-MAY-10; 02-FEB-25 ; AMENDMENT #7: 2008-JUN-13

8.0 TREATMENT PLAN

Although the National Cancer Institute of Canada Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

LHRH analog and antiandrogen must begin within 5 working days of patient randomization. Patients for whom orchietctomy is planned may be given LHRH analog while awaiting surgery. Patients receiving LHRH analog may begin antiandrogen either prior to or simultaneously with LHRH analog, keeping in mind that all treatment should not commence until after randomization.

8.1 Hormone Treatment Plan

Patients may be treated with any commercially available LHRH analog and antiandrogen during or after protocol treatment (Appendix IX). Patients may switch drugs at any time during or after protocol treatment.

For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare at each on-treatment interval. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician.

The antiandrogen and LHRH analog may be given on different dates. The time between LHRH analog injections should be kept to a practical minimum (e.g. +/- 7 days from expiry date of previous injection).

8.1.1 *IAS Arm (Intermittent Androgen Suppression)*

UK Centres - Patients randomized to the IAS arm must receive the monthly preparation of LHRH analog. Patients must not receive the three monthly preparation of LHRH analog if on the IAS arm.

8.1.1.1 *On-Treatment Intervals*

Patients on the IAS arm should receive a minimum of 4 weeks of antiandrogen and a total of 8 months of LHRH analog during each on-treatment interval. The dose and frequency of LHRH treatment will be determined by the drug being administered (Appendix IX). Patients on the IAS arm should not be given an LHRH analog injection at the end of month 8 unless the patient is transferred to continuous treatment as per protocol upon completion of the 8 month intermittent treatment (section 8.1.1.3).

Antiandrogen must be given for a minimum of 4 weeks to block tumour flare at the start of ***each*** on-treatment interval. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician

The first 8 month on-treatment interval must start within 5 working days of randomization.

Subsequent 8 month on-treatment intervals should be restarted when the patient meets the following criteria:

- PSA is > 10 ng/ml (μg/L)

AND

- There is no other evidence of clinical disease progression

IAS patients restarting after a non-treatment interval should restart an 8 month treatment interval expeditiously (e.g. within 2 weeks after PSA 10 ng/ml (μg/L) is noted.

8.1.1.2 *Non-Treatment Intervals*

A non-treatment interval is the time between 8 month treatment cycles for patients on the IAS arm. Upon completion of each 8 month treatment cycle, the patient must be assessed to ensure they meet the criteria to start a non-treatment interval. The duration of the non-treatment interval depends on the patient's PSA and absence of evidence of clinical disease progression.

Patients on a non-treatment interval should not receive LHRH analog or antiandrogen therapy. PSA and testosterone should be monitored every two months (section 9.0) during non-treatment intervals.

8.1.1.2.1 Starting a Non-treatment interval

Upon completion of an 8 month on-treatment cycle, patient may begin a non-treatment interval if <u>all</u> the following criteria have been met:

- PSA after 8 month treatment cycle is < 4 ng/ml (μg/L) AND < baseline PSA

<u>AND</u>

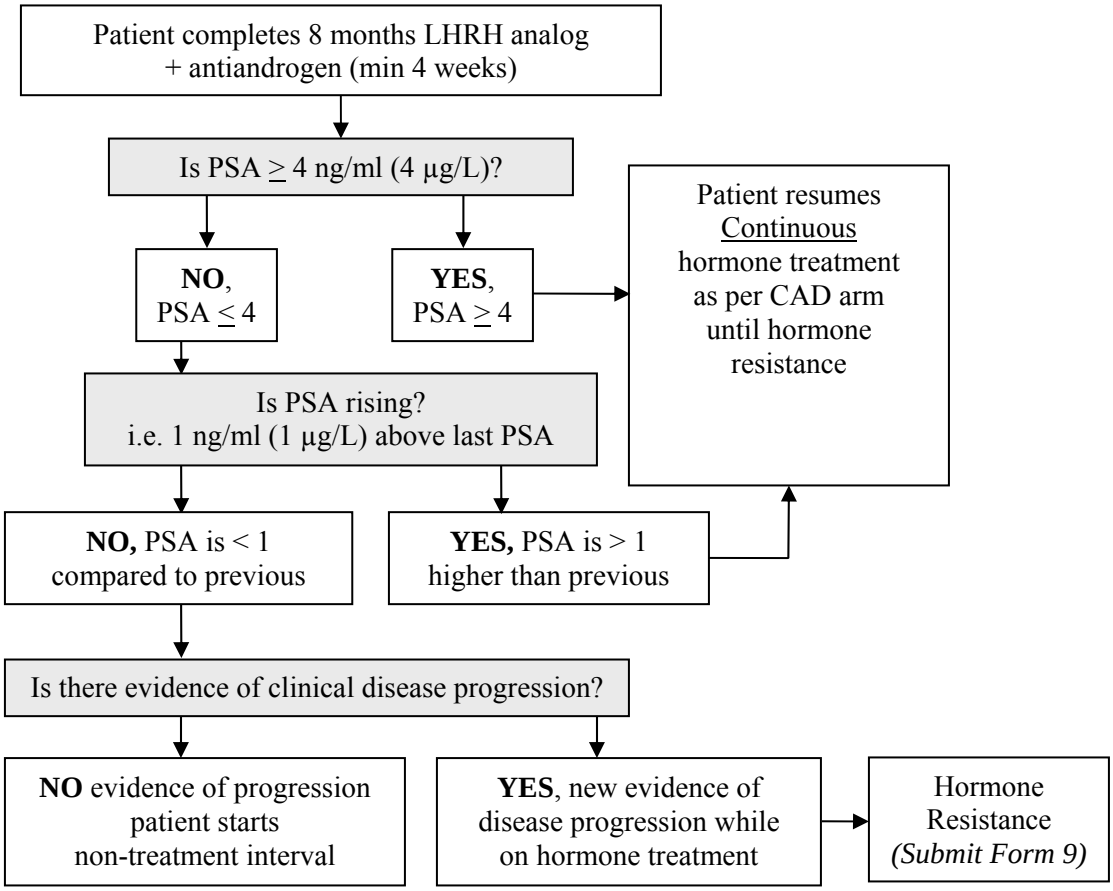
- PSA after 8 month treatment cycle is < 1 ng/ml (μg/L) above the previous on-treatment PSA i.e. PSA is not rising at the end of the treatment cycle

<u>AND</u>

- There is no other evidence of clinical disease progression

Patients who do not meet the criteria to start a non-treatment interval upon completion of an 8-month treatment cycle should be switched to continuous treatment (section 8.1.1.3)

PR.7 IAS ALGORITHM FOR STARTING OFF-TREATMENT INTERVAL



8.1.1.2.2 Remaining on a Non-treatment interval

Patients who meet the following criteria will continue on non-treatment interval:

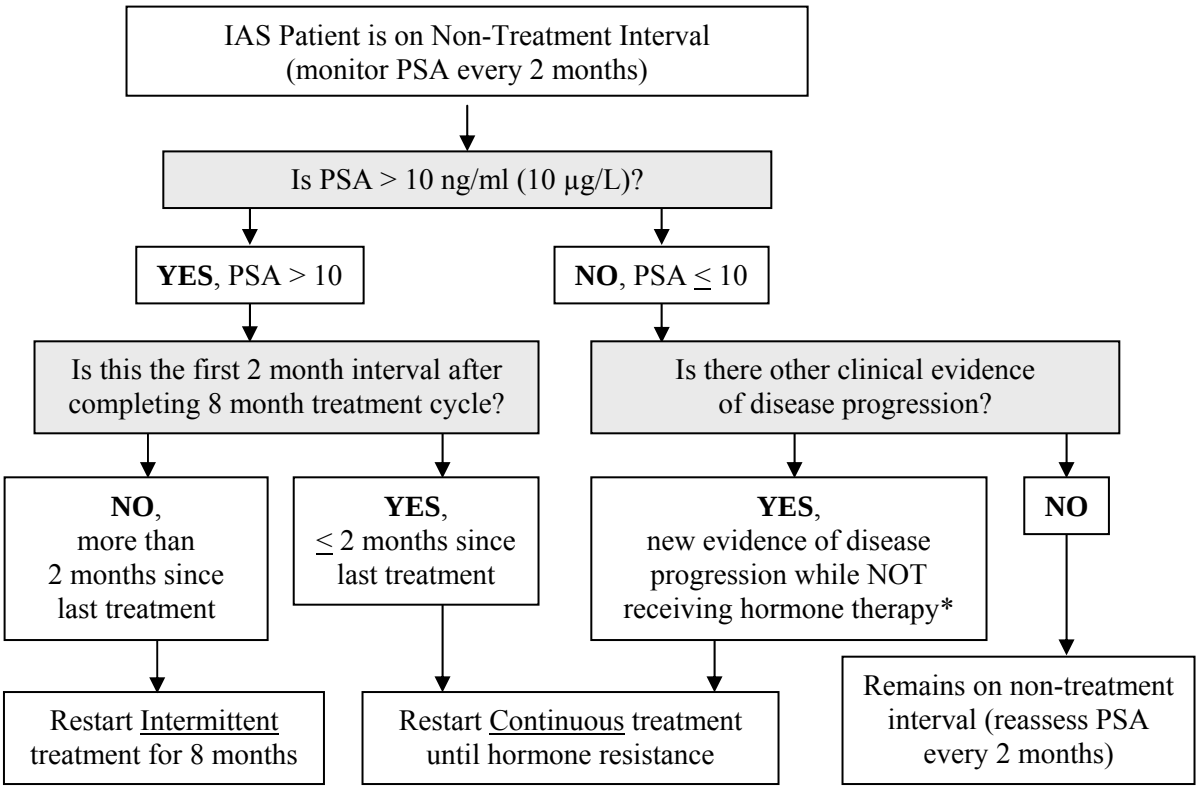
- PSA is ≤ 10 ng/ml (µg/L)

AND

- There is no other evidence of clinical disease progression

If a rise of > 1 ng/ml (µg/L) occurs during a non-treatment interval, continue to monitor PSA and testosterone every 2 months (without any hormone therapy), and restart treatment only when PSA is > 10 ng/ml (µg/L). A rise of > 1 ng/ml (µg/L) PSA is only a trigger to switch to continuous treatment when it happens at the end of the 8 month hormonal therapy.

PR.7 IAS ALGORITHM FOR RESTARTING TREATMENT



* Note: Hormone resistance cannot be declared during an off treatment interval. In the presence of new evidence of disease progression (i.e. distant metastases) hormone treatment according to the CAD arm (Section 8.1.2) should be given until criteria for hormone resistance have been met.

8.1.1.3 *Transfer to Continuous Treatment*

Patients who switch from IAS to continuous treatment should be followed according to the CAD Treatment Plan (section 8.1.2) until hormone resistance is documented.

Once switched to continuous treatment, the patient should not be evaluated for further non-treatment intervals.

Patients meeting any of these criteria should be transferred to continuous treatment

- There is evidence of clinical disease progression anytime during a non-treatment interval
- PSA is > 10ng/ml (µg/L) after the first two months of a non-treatment interval
- Final PSA of an 8-month on treatment interval is >1 ng/ml (µg/L) higher than the previous, on treatment PSA value (i.e. PSA is rising while patient is receiving hormone therapy)

IAS patients transferring to continuous treatment should resume hormone therapy as soon as possible.

8.1.2 CAD Arm (Continuous Androgen Deprivation)

Patients may be treated with any commercially available LHRH analog and antiandrogen during or after protocol treatment (Appendix IX). Patients may switch drugs at any time during or after protocol treatment.

The dose and schedule of treatment will depend on the agent used. Patients should continue to receive hormone therapy without interruption until hormone resistance has been documented (section10.3).

For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare at each on-treatment interval. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician

8.2 Treatment Modifications (both arms)

Drug dose escalation and reductions are not permitted on study. Substitution of drug with protocol specified antiandrogen and LHRH agonists are permitted at the discretion of the investigator.

8.2.1 *Antiandrogen*

For safety reasons the antiandrogen must be given for a minimum of four weeks at the beginning of LHRH analog to block tumour flare. Continuation of the antiandrogen beyond flare is optional and is permitted at the discretion of the treating physician.

Alternate antiandrogen (see Appendix IX) should be substituted or antiandrogen should be discontinued and not be restarted should a patient develop pneumonitis, dark urine and/or pruritus and hepatic damage confirmed by jaundice or an increase in any liver function test to greater than two times the upper normal limit. Liver function tests should be obtained at the first sign and symptoms suggestive of liver dysfunction, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia, “flu-like” symptoms, hyperbilirubinemia or bilirubinuria, jaundice or right upper quandrant tenderness.

Antiandrogen therapy should be discontinued in cases of unacceptable adverse events, as per the investigator's discretion.

Antiandrogen may also be restarted at the investigators discretion. Patients randomized to the CAD arm may restart antiandrogen therapy any time while receiving treatment with LHRH analog. Patients randomized to the IAS arm may restart antiandrogen therapy any time during an 8 month on-treatment interval.

Patients who discontinue the antiandrogen only are still considered on-study.

8.2.2 *Observation period*

If a patient stops protocol treatment (both LHRH analog and antiandrogen) or does not wish to restart treatment after the end of a non-treatment interval, for reasons other than hormone resistance (e.g. toxicity or patient refusal) the patient may have a further observation period of up to 8 months. An observation period may apply to patients randomized to either IAS or CAD arm. The patient may return to their allocated treatment (IAS or CAD) during the observation period. An observation period may last up to 8 months. After 8 months the patient must decide if he would like to start treatment or come off study. If the patient does not re-initiate therapy during this 8 month period they are then considered to have permanently discontinued protocol treatment on the date when the planned treatment was first not given (i.e. at the beginning of the observation period).

While the patient does not receive protocol treatment during an observation period, ongoing assessment of PSA is expected every 2 months as well as the other investigations listed in section 9.1.

Hormone resistance cannot be declared during an observation period

8.3 Concomitant Therapy

8.3.1 *Permitted*

- Lipid-lowering agents are allowed on this study. This trial collects fasting serum cholesterol and HDL/LDL from study entry until death. The use of these agents must be reported on the CRFs.
- The use of bisphosphonates during protocol therapy is permitted at the discretion of the investigator. The use of these agents must be reported on the CRFs.
- Megestrol acetate (Megace ®) may be used for treatment of hot flashes while the patient is on study. Its use must be reported on the CRFs.

8.3.2 *Not Permitted*

- Palliative radiation during protocol therapy may not be given as it implies clinical progression. Palliative radiation may be given at the discretion of the investigator after the criteria for hormone resistance has been met. For patients who develop bone metastases during a non-treatment interval, they will be considered off protocol therapy at the time palliative radiotherapy is given.
- The use of other hormonal agents during protocol therapy and prior to hormone resistance is strongly discouraged. The use of 5α-reductase inhibitors (e.g. Finasteride (Proscar ®),Dutasteride (Avodart®)) and any herbal remedies (e.g. Saw Palmetto, Angelica Sinensis) with potential anti-hormonal effects for prostate cancer are strongly discouraged while on study, including during the off-treatment intervals and observation periods .
- The use of any non-protocol agents with potential anti-hormonal effects for prostate cancer prior to hormone resistance should be discussed with NCIC CTG prior to administration.
- Administration of any other anti-cancer therapy (cytotoxic, biological/immunotherapy or radiotherapy) is not permitted while the patient is receiving protocol therapy. Thereafter patients may be treated at the investigator's discretion.
- Other investigational drug therapy is not permitted while the patient is receiving study medication.

REVISED: 98-DEC-15; AMENDED: 99-JUN-04; 00-JUL-18; 02-FEB-25; AMENDMENT #7: 2008-JUN-13

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

Patients who discontinue protocol therapy for reasons other than hormone resistance should continue to have their PSA monitored closely for hormone resistance. Any further non-protocol hormone treatment must be reported on the CRFs.

If patients permanently discontinue protocol treatment and/or are removed from therapy because of hormone resistance, further treatment is at the discretion of the investigator. Patients will continue to have follow-up until the time of death

9.1 Evaluation DURING Protocol Treatment
(including non-treatment intervals and observation periods)

Investigations		Timing Prior to Hormone Resistance
History and Physical Exam including:	ECOG Performance Status Weight	Every four months for the first 2 years and then every 8 months
Biochemistry	PSA Serum testosterone (not free testosterone)	Every 2 months
	Total bilirubin Alkaline phosphatase LDH AST (SGOT) ALT (SGPT)	Monthly while patients are receiving antiandrogen therapy
	Fasting Serum cholesterol - total / HDL / LDL	Annually
Hematology	Hemoglobin	Annually
Radiology	Bone scan	Annually
	Chest X-ray	As clinically indicated
Adverse events	Patients must be evaluated continuously for adverse events*	Every four months for the first 2 years and then every 8 months
Quality of Life	EORTC QLQ-C30 and Trial Specific Questionnaire	
Concomitant Medications	Lipid-lowering agents Bisphosphonates Other hormonal agents	
Other Investigations	Blood sample (see 13.1) (NCIC CTG Centres Only)	CAD Arm: Annually for 5 years
	Additional Blood Sample for RT-PCR testing (Toronto centres only)	CAD Arm: Annually for 5 years IAS Arm: Beginning and end of each non- treatment interval
* Adverse events will be recorded and graded according to the Common Toxicity Criteria Version 2.0 (Appendix V)		

9.2 Evaluation At The TIME OF HORMONE RESISTANCE

Investigations		Timing
History and Physical Exam:	ECOG Performance Status	At hormone resistance
Biochemistry	PSA	In the absence of new evidence of disease, 3 rises in PSA (4 PSA values each at least 1 month apart) required to meet the criteria for hormone resistance (see section 10.3)
	Serum testosterone (not free testosterone)	At hormone resistance Castrate levels of testosterone (< 3 nmol/L or < 85 ng/dl) within 6 weeks of date of hormone resistance (see section 10.3)
	Fasting serum cholesterol - total/HDG/LDL	At hormone resistance
Hematology	Hemoglobin	At hormone resistance
Radiology	Bone scan	As clinically indicated
	Chest X-ray	As clinically indicated
Quality of Life	EORTC QLQ-C30 and Trial Specific Questionnaire	At hormone resistance
Other Investigations	Blood sample (see section 13.1) (NCIC CTG Centres Only)	At hormone resistance for IAS Arm only

9.3 Evaluation AFTER Protocol Treatment

9.3.1 *Off Treatment for Any Reason Other Than Hormone Resistance*

Investigations		Timing Prior to Hormone Resistance
History and Physical Exam		Every four months for the first 2 years and then every 8 months
Biochemistry	PSA Serum testosterone (not free testosterone)	Every 2 months
	Fasting Serum cholesterol - total /HDL/LDL	Annually
Radiology	Bone scan	Annually
	Chest X-ray	As clinically indicated
Adverse events	Patients must be evaluated for delayed adverse events of protocol therapy	every 8 months
Quality of Life	EORTC QLQ-C30 and Trial Specific Questionnaire	Every four months for the first 2 years and then every 8 months
Concomitant Medications	Lipid-lowering agents Bisphosphonates Other hormonal agents	every 8 months
Other Investigations	Blood sample (see section 13.1) (NCIC CTG Centres Only)	CAD arm Only: annually for 5 years from randomization

9.3.2 *Evaluation After Hormone Resistance*

Investigations		Timing After Hormone Resistance
History and Physical Exam		Annually
Biochemistry	PSA Fasting Serum cholesterol - total /HDL/LDL	Annually
Adverse events	Patients must be evaluated for delayed adverse events of protocol therapy	
Quality of Life	EORTC QLQ-C30 and Trial Specific Questionnaire	
Other Investigations	Blood sample (see 13.1) (NCIC CTG Centres Only)	CAD Arm: Annually for 5 years
	Additional Blood Sample for RT-PCR testing (Toronto centres only)	CAD Arm: Annually for 5 years

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

Evaluability for Endpoints

All patients are evaluable for the endpoints from the first day of hormone therapy and the completion of the first assessment of each endpoint.

10.1 Overall Survival

Survival, defined as the time from randomization to the time of death (from any cause) or to the last follow-up is the primary endpoint of the study.

10.2 Time to the Development of Hormone-Resistance

The time until hormone resistance develops is taken as the time from randomization to the development of hormone-resistance as defined in 10.3. This time period has been proposed as a surrogate endpoint for prostate cancer death[25].

10.3 Hormone-Resistance

Hormone resistance criteria can only be met while the patient is receiving hormone treatment. Patients who have undergone an orchiectomy are considered to be on treatment for the purpose of declaring hormone resistance. For IAS patients on a non-treatment interval, please follow section 8.1.1. For CAD or IAS patients on an observation period please see section 8.2.2.

10.3.1 *Definition of Hormone Resistance*

Hormone-resistance has occurred when a patient has:

A bilateral orchiectomy or has castrate levels of testosterone (< 3 nmol/L) (85 ng/dl) measured within 1½ months (six weeks) of the qualifying event (see section 10.3.2).

AND

Three successive increases in PSA (one month or more apart and during treatment) with the highest PSA $\geq$ 4 ng/ml (4 μg/L).

AND/OR

New evidence of clinical disease.

Three successive increases in PSA:

- Three increases in PSA requires comparison of four PSA values
- All four PSA values must be taken while on treatment (patient must be receiving LHRH analog +/- antiandrogen or have had an orchiectomy)
- Each PSA value in the comparison must be at least one month apart
- At least one PSA must be $\geq$ 4.0 ng/ml ($\geq$ 4.0 μg/L)
- A minimum increment level of > 0.4 ng/ml (> 0.4 μg/L) between each increase is recommended. While no minimum increase is proscribed, in order to avoid an erroneous declaration of a rise in PSA as a result of test variability, the minimum increment between any PSA readings should be considered sufficient to declare a PSA rise.
- Successive increases occur on three or more dates. They do not need to take place on consecutive dates, but the trend of the PSA levels must be increasing over time.

Evidence of new clinical disease:
In the absence of a rising PSA level, new evidence of clinical disease must be unequivocal in the opinion of the investigator. Thus sites of increased uptake of isotope on bone scan should ideally be multiple, asymmetrical and confirmed by x-ray changes at least one site. Reasonable care should also be taken to eliminate a second cancer at the common primary sites of such cancers.

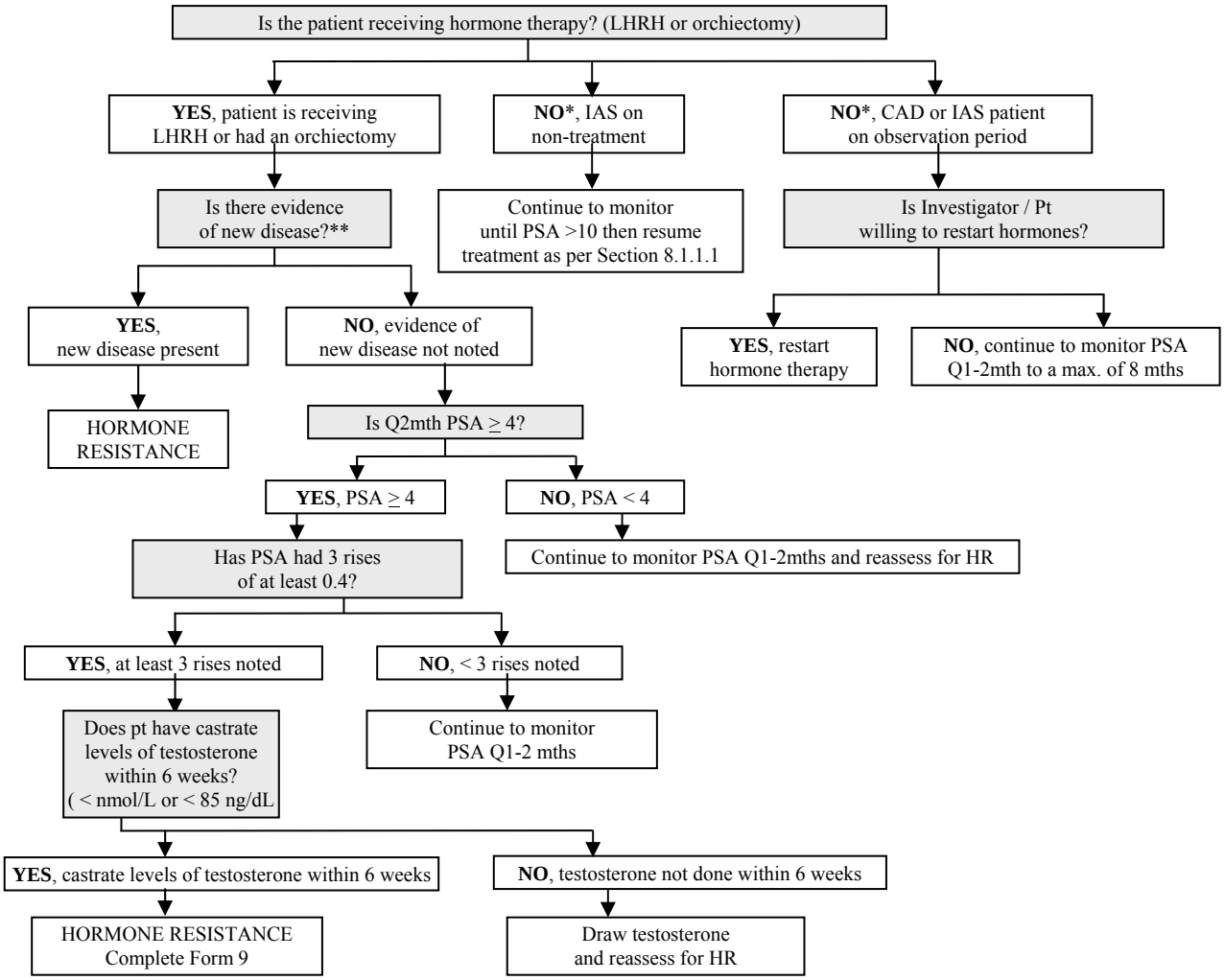
Local prostate enlargement should not be considered evidence of new clinical disease.

10.3.2 *Date of Hormone Resistance*

Date of hormone resistance will be considered to be the date the first PSA is ≥ 4 ng/ml (4 µg/L), or the date of first evidence of new clinical disease, whichever is earliest. This date may be determined retrospectively and is not necessarily the same as the date protocol treatment is stopped.

Hormone resistance criteria can only be met while the patient is receiving treatment. During an off-treatment interval please follow the algorithm in section 8.1.1.

PR.7 Algorithm for Hormone Resistance:



Notes:
* Patient must be receiving hormone therapy to meet criteria for hormone resistance.
** In the absence of rising PSA level, new evidence of clinical disease must be unequivocal in the opinion of the investigator.

10.4 Quality of Life

This is a secondary endpoint for the trial. See section 14.3 for summary of the analysis of quality of life.

10.5 Serum cholesterol/HDL/LDL levels at 3 years

These levels annually and the differences between these levels at three years and those at baseline in the same patients will be compared between the two arms.

10.6 Descriptive Endpoints on the IAS Arm

- Duration of treatment and non-treatment intervals.
- Time to testosterone recovery, as documented by serum testosterone returning to pre-treatment levels.
- Time to recovery of potency, as documented by QOL questionnaires.

10.7 Number of CAG Repeats on Androgen Receptors

Number of CAG repeats on the androgen receptor measured in the DNA of the blood samples.

11.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of this commercially available treatment should be reported to NCIC CTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified (except UK centres).

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 2.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 2.0.

All serious adverse events (SAE) defined as per ICH guidelines (see section 11.1) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the NCIC CTG - Serious Adverse Event Report forms (Canadian Centres), the AdEERs reporting system (CTSU AND SWOG centres see section 11.2.2), or the UK Serious Adverse Event (SAE) form (ICR-CTSU Centres), as defined below.

11.1 Definition of a Reportable Serious Adverse Event (SAE)

- All serious adverse events, which are unexpected and related to protocol treatment, must be reported in an expedited manner (see section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the product monograph or package insert.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

11.2.1 *NCIC CTG Participating Centres Responsibilities*

All reportable serious adverse events as defined in Section 11.1 must be reported as follows:

Within 24 hours	FAX preliminary Serious Adverse Event Form to: Dr. Chris O'Callaghan, Project Coordinator or PR.7 Study Coordinator NCIC Clinical Trials Group Fax: 613-533-2941
Within 10 days	Mail NCIC CTG Serious Adverse Event Report form (signed by the investigator and updated as much as possible) to: NCIC Clinical Trials Group Queen's University 10 Stuart Street Kingston, Ontario K7L 3N6

11.2.2 *US Participating Centres Responsibilities (SWOG and CTSU)*

All Southwest Oncology Group (SWOG) investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines.

U.S. investigators should report serious adverse events via the NCI's Adverse Event Expedited Reporting System (AdEERS).

Information regarding the use of AdEERS can be found at: http://ctep.cancer.gov. The NCI's guidelines for AdEERS can also be found at the same website.

The commercial agents used in this protocol are listed in Appendix IX. AdEERS is programmed to send submitted commercial agent expedited reports directly to the FDA.

Copies of reports for this trial submitted via the AdEERS web application will be automatically forwarded by the AdEERS system to the NCIC CTG Central Office for review. You may be contacted by the NCIC CTG Study Coordinator or Physician Coordinator for additional information.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

AdEERS web application interruption:
In the rare event that internet connectivity to the AdEERS system is disrupted, a paper template (Adverse Event Expedited Report – Single Agent or Multiple Agent Form as applicable for your trial) may be obtained from the CTEP Home Page at: http://ctep.cancer.gov. Please complete ALL sections as required.

For 24-hour notifications, please report to CTEP by telephone at: 301-897-7497. For all other reports, fax templates to CTEP at 301-230-0159.

All reports must also be faxed within 24 hours to:

PR.7 Study Coordinator
NCIC Clinical Trials Group
Fax No.: 613-533-2941

Once internet connectivity is restored, the original submitter of the SAE report that was faxed to CTEP on a paper template or that was reported by phone to CTEP as a 24-hour notification, must enter the event into the AdEERS web application.

Local internet interruption:
A paper template (Adverse Event Expedited Report – Single Agent or Multiple Agent Form as applicable for your trial) may be obtained by calling CTEP at: 301-897-7497. In cases of prolonged internet interruptions, please contact the NCIC CTG Safety Desk for further instructions (613-533-6430).

11.2.2.1 AdEERS Reporting Requirements for Commercial Agents (not under an IND)

All grade 4 and 5 unexpected and related (i.e. possibly, probably or definitely) reactions (not reported in the PM) must be reported via AdEERS within 3 calendar days of the event. (see table below).

Table: Expedited reporting requirements for adverse events experienced by patients who have received commercial drug(s) on this study.

Attribution	Grade 4		Grade 5*	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely				
Possible, Probable, Definite	AdEERS		AdEERS	

AdEERS: Indicates an expedited report is to be submitted using the NCI AdEERS Commercial Drug pathway within 3 calendar days of learning of the event.

* According to the instructions above, an expedited report must be submitted for death attributed (possibly, probably, or definitely) to the commercial agent(s) regardless of date from last treatment and is not due to cancer recurrence.

In addition all grade 1, 2 or 3 events that are serious (as defined in section 11.1), and meet the criteria above (unexpected and related) must also be reported via AdEERS. For these events, please include the following statement in the Description of Event section: "A protocol specific requirement has contributed to the reporting of this event."

11.2.3 *UK Participating Centres Responsibilities*

All reportable serious adverse events as defined in Section 11.1 must be reported by the investigators to the ICR-CTSU as follows:

Within 24 hours
Report event by fax to:
Rosa Lau, Data Manager Fax: 020-8720-7876

The Clinical Trials and Statistics Unit of the ICR-CTSU will then notify the NCIC CTG by fax within 24 hours.

Within 3 days
Mail the completed UK Serious Adverse Event (SAE) form to:
Rosa Lau, Data Manager
The Institute of Cancer Research
Section of Clinical Trials
Clinical Trials and Statistics Unit (ICR-CTSU)
Sir Richard Doll Building
Cotswold Road
Sutton, Surrey SM2 5NG, UK

Tel: 020 8722 4152 / Fax: 020 8770 7876

The Clinical Trials and Statistics Unit of the ICR-CTSU will then mail the completed SAE form to NCIC CTG immediately upon receipt from investigators.

11.3 Reporting Secondary Malignancies or Myeloid Dysplasias

11.3.1 *Canadian and UK Reporting Responsibilities*

Canadian and UK centres should report secondary malignancies that meet the criteria in section 11.1 (serious, unexpected and related to protocol treatment) by submitting an NCIC CTG SAE report.

11.3.2 *U.S. Reporting Requirements*

Secondary malignancies or myeloid dysplasia that meet the criteria in section 11.1 (unexpected AND related to protocol treatment) must be reported to NCI U.S. via AdEERS in an expedited manner. For these events, please include the following statement in the Description of Event section: "A protocol specific requirement has contributed to the reporting of this event".

For SWOG Centres - Reporting Acute Myeloid Leukemia (AML)/Myelodysplastic Syndromes (MDS)

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/MDS/ALL diagnosis; and
- (if available) a copy of the cytogenetics report.

Submit the Report and documentation to: CTEP

by fax to: 301-230-0159

or mail to	Investigational Drug Branch ATTN: SAE Program P.O. Box 30012 Bethesda, MD 20824-0012	and	Southwest Oncology Group 14980 Omicron Drive San Antonio, Texas 78245-3217

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the AML/MDS Report must be submitted for the most recent trial'

11.4 Reporting Serious Adverse Events to Local Ethics Boards

NCIC CTG will notify all Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report in their study files.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/ REB name;
- the date of REB submission must be provided;
- this form must be signed by one of the approved participants (according to the participants list) for this trial.

The submission of these events to your ethics board should be done as soon as possible. It is expected that these will be submitted for review within 30 days of the date of the letter to the investigator.

For UK Investigators
In the UK, the ICR-CTSU will report unexpected and related SAEs to the MHRA and MREC only. ICR-CTSU will also inform all Primary Investigators of any reportable SAEs but they are not required to notify their local research ethics committees.

11.5 NCIC CTG Reporting Responsibilities

11.5.1 *NCIC CTG Reporting Responsibilities for Reporting Serious Adverse Events to Health Canada (Office of Clinical Trials and Marketed Health Products Directorate (MHPD))*

The NCIC CTG will provide expedited reports of SAEs to Health Canada ((Office of Clinical Trials and Marketed Health Products Directorate (MHPD)) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Investigator Brochure), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

11.5.2 *Reporting Responsibilities for Reporting Serious Adverse Events to U.S. Regulatory Authorities*

All reportable events occurring in U.S. patients will be reported to the FDA at the time the AdEERs report is submitted. NCIC CTG will notify SWOG and CTSU of all reportable events which occur for this trial on non-U.S patients. SWOG and CTSU are responsible for reporting the international events to the relevant US regulatory agencies.

11.5.3 *Reporting Responsibilities to the Multi-Centre Research Ethics Committees (MREC) of the National Health Service (NHS) and the Medicines and Healthcare Products Regulatory Authority (MHRA) in UK*

The ICR-CTSU Trials Office will forward SAEs to the UK Multi-Centre Research Ethics Committee (MREC) of the National Health Service (NHS) and the Medicines and Healthcare Products Regulatory Authority (MHRA) in UK as required.

NCIC CTG will notify ICR-CTSU of all reportable events which occur for this trial on non-UK patients.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

Patients who permanently stop hormone therapy as mandated by the protocol are considered to be off-protocol treatment.
Patients who are not taking hormones are still considered on protocol therapy in the following instances:

- IAS patients on a non-treatment interval
- IAS or CAD patients on an observation period (maximum of 8 months) (see section 8.2.2)
- Patients who stop antiandrogen therapy because of adverse events but who continue to receive treatment with LHRH analog
- Patient who permanently stop LHRH analog because they have had an orchietomy

Patients who permanently discontinue protocol therapy prior to hormone resistance are still considered to be on study and must still be followed according to section 9.3.1 *Off Treatment for Any Reason Other Than Hormone Resistance* in order that their data may be included in the secondary endpoint of time to hormone resistance.

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- The diagnosis of hormone-resistance (see section 10.3)
- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree, and/or would require discontinuation of protocol therapy.
- Unacceptable toxicity from the LHRH analog (if toxicity is due to antiandrogen only see sections 8.2.1 and 8.2.2).
- Request by the patient.
- The use of palliative radiotherapy before hormone-resistance.

12.2 Therapy After Protocol Treatment is Stopped

Following the development of hormone-resistance or any of the other causes of permanent cessation of protocol treatment given in section 12.1 subsequent therapy is entirely at the discretion of the investigator. All therapies given for the treatment of prostate cancer, including: hormonal therapy, anticancer/cytotoxic agents and radiotherapy must be recorded on the CRFs (Form 5 for patients prior to hormone resistance and Form 5S for patients after hormone resistance).

12.3 Follow-Up Off Protocol Treatment

The extent of follow up required after permanent discontinuation of protocol therapy depends on the status of the patient's prostate cancer. Patients who permanently stop protocol therapy for any reason other than hormone resistance should be followed according to sections 9.3.1 and 12.3.1 until the criteria for hormone resistance have been met, even if this occurs after the discontinuation of protocol therapy.

Once the criteria for hormone resistance (section10.3) have been met, less intensive follow up is required. Patients who have documented hormone resistance may be followed according to sections 9.3.2 and 12.3.2 until death.

12.3.1 *Follow-Up Off Protocol Therapy PRIOR To Hormone Resistance*

All patients who permanently stop protocol therapy for any reason other than hormone resistance must continue to be followed closely for hormone resistance. This includes attending regularly scheduled follow-up visits and PSA and other evaluations as outlined in section 9.3.1. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.3.2 *Follow-Up Off Protocol Therapy AFTER Hormone Resistance*

Patients who have met criteria for hormone resistance will be followed annually from randomization until death, according to section 9.3.2.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if no longer attend the participating institution.

13.0 CENTRAL REVIEW PROCEDURES

There will be no central pathology review in this study.

13.1 Translational Research

A Prospective Search for Blood Markers as Predictive Factors (for NCIC CTG centres only)

Blood samples for translational research will be collected and sent to a central lab for analysis.

Samples will be sent to:

CIRION Biopharma Research Inc.
Clinical Trials Services
2121 Berlier Street
Laval, QC H7L 3M9

Telephone: 450-688-6445 ext 231 or 1-800-651-5005

Fax: 450-902-3254 or 1-888-902-3254

13.2 Collection Schedule

Canadian patients randomized to the CAD arm: Serum collection for CAG trinucleotide, IGF, and oxidative stress testing is required pre-treatment and annually for 5 years.

VISIT SCHEDULE - *CAD ARM ONLY*						
EVALUATIONS	Pre-treatment	Month 12	Month 24	Month 36	Month 48	Month 60
CAG Trinucleotide	X					
IGF	X	X	X	X	X	X
Oxidative Stress	X	X	X	X	X	X

Canadian patients randomized to the IAS arm: Serum collection for CAG trinucleotide, IGF, and oxidative stress testing are required pre-treatment. Serum for oxidative stress and IGF are required at the time criteria for hormone resistance is met (section10.3)

VISIT SCHEDULE - *IAS ARM ONLY*		
EVALUATIONS	Pre-treatment	Hormone Resistance
CAG Trinucleotide	X	
IGF	X	X
Oxidative Stress	X	X

13.3 Specimen Requirements

SPECIMEN REQUIREMENTS			
TEST	COLLECT	PREPARE	SUBMIT
CAG Trinucleotide	(1) 7 mL Mauve	Mix well	1 Lavender Top Tube (cold pack)
IGF Oxidative Stress	(1) 10 mL Plain Red	Spin the sample and pipette the clear yellow serum into the plastic transport vial provided.	1 Plastic Transport Vial (cold pack)

13.4 Order of Tubes

It is very important that the tubes be collected in this order. This allows minimal amount of contamination of anticoagulant from tube to tube.

1. First PLAIN RED TUBE
2. Second LAVENDER TUBE

13.5 Laboratory Operations Manual

Please refer to manual provided by CIRION Biopharma Research for instructions on specimen collection and shipping.

13.6 RT-PCR for Toronto centres only

For patient randomized to the CAD arm by Toronto Sunnybrook Regional Cancer Centre and the Princess Margaret Hospital an additional 8 ml blood sample will be required for RT-PCR testing pre-treatment and annually for 5 years while on study. The serum collection is not required for patients who have permanently stopped protocol therapy for any reason prior to 60 months.

This additional collection is required at

IAS Arm - Pretreatment - 28ml + 8 ml = 36 ml total
- Beginning and end of each non-treatment interval - 8 ml total

CAD Arm - Pretreatment - 28ml + 8 ml = 36 ml total
- Annually for 5 years - 19 ml + 8 ml = 27 ml total

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Study Design

The primary objective of the study is to compare overall survival between intermittent versus continuous androgen deprivation for prostate cancer patients with biochemical failure after radiotherapy in order to assess equivalence in efficacy. Patients will be randomized with equal probability to one of the two treatment arms, stratification will be performed prior to randomization. Stratification factors include time since radiotherapy (> 1 to 3 years vs. ≥ 3 years), initial PSA level (3 ng/ml to 15 ng/ml vs. > 15 ng/ml or 3 μg/L to 15 μg/L vs. > 15 μg/L), prior radical prostatectomy (Yes vs. No), prior neo-adjuvant, concurrent, or adjuvant cytoreduction in association with the radical radiotherapy treatment or prostatectomy for a maximum duration of 12 months and completed at least 12 months prior to randomization (Yes vs. No).

14.2 Primary Endpoint and Analysis

The primary endpoint for this study is survival, defined as the time from randomization to the time of death from any cause or last follow-up. Log-rank statistics will be used to compare survival experience between the two arms. A Cox proportional hazards model will be used to assess prognostic factors, and the treatment effect will be tested after controlling for important prognostic variables.

14.3 Secondary Endpoint and Analysis

Time to hormonal resistance will be used as a secondary endpoint. This is defined as time from randomization to the time of evidence of hormone resistance. Date of hormone resistance will be considered to be the date the first PSA is ≥ 4.0 ng/ml (≥ 4.0 μg/L) or the date of first evidence of new clinical disease, whichever is earliest.

Hormone-resistance has occurred when a patient who has had a bilateral orchiectomy or has castrate levels of testosterone (< 3 nmol/L) (< 85 ng/dl)measured within 1½ months (six weeks) of the qualifying event (the first PSA level > 4.0 ng/ml (4 μg/L) or the date of new clinical disease).

AND

Three successive increases in PSA

AND/OR

Evidence of new clinical disease.

Since early comparison between treatment arms with respect to time to hormonal resistance may compromise the assessment of the primary endpoint through potential changes in practice or degeneration of follow-up efforts, the results of this secondary endpoint would not be disclosed during the study except for the purpose of a formal interim analysis. At the time of formal interim analysis, the Data and Safety Monitoring Committee will be designated to review this data and results will be kept confidential prior to the completion of the study.

For quality of life, we will use EORTC QLQ-C30 which contains a global QOL domain and five functioning domains plus other symptom domains and checklist. First, we are interested to test the difference in the global QOL change score from baseline between the two treatment arms. We would then evaluate the other functioning domains and symptoms to further understand the impact of the intermittent treatment. The quality of life scores will be analyzed using an analysis of variance model with repeated measures.[26] For the trial specific checklist, they are single items in the form of repeat categorical data, and will be analyzed using the generalized least squares method proposed by Koch et al (1977).[27]

Serum cholesterol/HDL/LDL levels will be compared using two-sample t-test. The effect of treatment on bone density will be explored by a mixed effect model. The duration of treatment and non-treatment intervals, time to testosterone recovery and time to recover of potency will be analysed using a Cox regression model.

14.4 Sample Size and Duration of Study

The sample size of this study is calculated using a one-sided test of equivalence as suggested in Lin (1995)[28] and Willan (1994).[29] We assume that the median survival for the continuous androgen deprivation arm (CAD) is 7 years. The treatment difference (D) is defined as the survival probability at 7 years for the CAD arm minus that of the intermittent androgen suppression arm (IAS). We would consider the IAS to be equivalent to the CAD arm if we were 95% sure that the true difference was less than 8% (i.e. δ_{IAS}=0.08; the upper bound of a 90% CI exclude 0.08). This boundary for the difference can be translated to a boundary for the hazards ratio of 1.25. In order to reject the hypotheses with 80% power at 5% level assuming that we are using a point of indifference at 4%, we need to enter a total of 1340 patients. If the accrual rate is 300 patients per year, the total accrual time would be about 4.5 years. The required number of events for this study is determined to be about 800 which would be obtained after 7 years of follow-up.

A recent paper by Osoba et al. (1998)[32] has determined the relationship between global quality of life change score and results from a "subjective significance questionnaire". These results provide us with some evidence that patients are capable of identifying subjective change in their quality of life and a change score of 7-10 points out of a 100 in the global quality of life domain is an acceptable range to use. According to our previous studies, the standard deviation for global quality of life change score is about 25-35. In order to detect a difference of 7-10 points change in this study with 80% power using a two-sided 5% level test, we need a total of 600 patients assuming a standard deviation of 30 and to detect a difference in change score of 7. The following table shows the total number of patients with various parameters:

	Standard Deviation		
d	25	30	35
7	400	578	787
8	307	442	602
9	242	350	476
10	197	238	386

14.5 Interim Analysis

A formal interim analysis for equivalence study, using the method as suggested by Freedman, Lowe and Macaskill (1984)[30] with the O'Brien and Fleming boundary,[31] is planned. The results of this analysis will be presented to the Data and Safety Monitoring Committee (DSMC) of the NCIC CTG. An early-stopping decision in favour of IAS would be considered if we were 99.5% sure that the true difference was less than 8%, or in terms of hazards ratio, that if we were 99.5% sure that the true hazards ratio was less 1.25 (i.e., the upper bound of the 99% confidence interval for the hazards ratio was less than 1.25 and the lower bound of the 99% CI were less than one). An early-stopping decision in favour of CAD arm would be considered should it be 99.5% sure that the lower bound of the hazards ratio is greater than one and the upper bound exceeds 1.25. Otherwise, the study will be carried out to the target sample size and duration. The total number of events in this study is estimated to be about 800. We would perform the planned interim analysis when we observed a total of 400 events in the study. The calendar time to get 400 events is about one year after the completion of accrual. This procedure will provide us with less than a 5% chance of making a false decision on the appropriate treatment with respect to the defined criteria. Safety data will be monitored annually by the DSMC.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc.

15.1.1 Prior to trial activation, the chairs will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first authors will generally be the chairs of the study. Dr. Crook followed by the other chairs of the study.
- The first author for the QOL outcome will generally be the QOL Coordinator for this component of the study.
- A limited number of the members of the NCIC Clinical Trials Group (NCIC CTG), the Southwest Oncology Group (SWOG), the Radiation Therapy Oncology Group (RTOG), and the National Cancer Research Institute (NCRI) Prostate Clinical Study Group and/or the Clinical Trials and Statistics Unit of the Institute of Cancer Research (ICR-CTSU), may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chairs.

15.1.2 In an appropriate footnote or at the end of the article the following statement will be made:

> "A joint study of the NCIC CTG, SWOG, CTSU and Cancer Research UK, coordinated by the Clinical Trials Group of the National Cancer Institute of Canada. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the study chairs to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG physician and study coordinator, and approval of all the study chairs. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Institution Eligibility for Participation

All member centres in good standing of the NCIC CTG, SWOG, CTSU or ICR-CTSU are eligible to participate in this study. Institutions which are not NCIC CTG members can either make application for membership or submit a single study agreement document. Any centre joining the NCIC CTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

Because this trial is affected by U.S. legislation, U.S. federal regulations for the protection of human subjects apply. Canadian and U.S. institutions must have a Federalwide Assurance (FWA) number issued by the Office for Human Research Protections (OHRP) of the Department of Health and Human Services. By means of this assurance, the institution and its REB agree to abide by U.S. standards regarding, for example, constitution of the REB/IRB.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the NCIC CTG:

- Current curriculum vitae, updated and submitted within two years at the time of randomization.
- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).

16.3 Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to NCIC CTG studies. It is the responsibility of NCIC CTG to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

NCIC CTG will notify all the trial investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.4 REB (Research Ethics Board) Approval for Protocols

Each NCIC CTG participating centre will have on file with the NCIC CTG central office, as part of its membership/ agreement documents, a description of its ethics review process.

Initial Approval
Member centres wishing to participate in a trial are required to obtain local ethics approval of the protocol and consent form (see below) by the appropriate REB.

Annual Re-Approvals
This trial is NCI US affiliated and therefore U.S. regulations regarding the Protection of Human Subjects apply (U.S. Code of Federal Regulations Title 45, Part 46). These regulations require that re-approvals of research be conducted at least once per year for as long as data are being submitted on trial patients, even through the follow-up period. Furthermore, these regulations require that annual re-approvals must be full board as long as the study is open to accrual or patients are receiving protocol treatment or undergoing protocol mandated interventions.

Amendments/Administrative Updates

All amendments or administrative updates to the protocol must undergo review by local REB/IRBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB/IRB review. If full board approval of an amendment is required it will be specified.

16.5 Ethics Approval for UK Institutions

The trial has obtained approval by the London Multi-Centre Research Ethics Committee (MREC) (MREC 01/2/63). Before entering patients into the study, clinicians must ensure that the protocol has received Site Specific Assessment (SSA) from their Local Research Ethics Committee (LREC). The patient's consent to participate in the study should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment, and the manner of treatment allocation.

The right of the patient to refuse to participate without giving reasons and without prejudicing his further treatment must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patient's best interest. However, the reasons for doing so should be recorded and the patient will need to remain within the study for purposes of follow-up and data analysis according to the treatment.

EU Regulatory Requirements

Intercontinental trial falls under the scope of the EU directive on Clinical trials and has a Clinical Trial Authorisation (CTA Number 15983/0006/001) from the UK Medicine Healthcare products Reglulatory Authority (MHRA).

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the investigational medicinal product (IMP).

For the purposes of MREC approval, the study end date is deemed to be the date of the last data capture.

MREC: /01/2/63
ISRCTN: 22761545
EUDRACT: 2004-000094-64

16.6 Informed Consent

Informed Consent Document

The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB notification/approval.

For studies affected by U.S. legislation, U.S. regulations regarding consent forms apply. The OPRR lists the following elements which must be addressed in each institution's consent form:

I. Required (by OPRR) Elements - Must be present in the informed consent document.

1. a. Clearly state that the study involves research.
   b. State which drug(s), treatment(s), or delivery technique(s) is experimental.
   c. Clarify the study purpose(s) in layman's terms.
   d. State the patient's expected duration of participation in study (e.g., the patient will be treated until there is evidence that therapy is no longer effective).
   e. Give a brief description of the procedure(s) to be performed to monitor the patient during study (e.g. X-rays, lab evaluations, etc.). An exhaustive list is not necessary.
   f. Give a description of the experimental aspect(s) or new delivery technique(s) of the study.
   g. State in specific terms the route of administration of each drug (e.g. IV, oral, continuous infusion, etc.).
   h. State estimated time of delivery of each drug or time of procedure (e.g. 5 minutes, 30 minutes, 24 hours, etc.).
2. State which risks are attributed to specific drug(s) or procedure(s).
3. Clarify and describe expected benefit(s) to be derived from participation in this study (e.g. tumour shrinkage, quality of life, etc.).
4. In general terms, discuss alternative treatment(s) to participation in this study (e.g. conventional chemotherapy, irradiation, hormonal therapy, surgery, etc.).
5. a. State the extent to which confidentiality of records will be maintained.
   b. State that a qualified representative of the FDA may inspect patient/study records.
   c. State that a qualified representative of the NCI may inspect patient/study records.
6. a. State if compensation for study related injury will be provided by the institution or other insurer.
   b. State if emergency treatment of injury will or will not be provided by the institution.
7. a. Provide space in the form or list the name(s) and number(s) of contact person(s) for research related questions.
   b. Provide space in the form or list the name(s) and number(s) of contact person(s) (not involved in the research) for patient rights related questions.
8. a. Clearly state participation is voluntary.
   b. State that refusal to participate will involve no loss of benefits or penalize the patient's care.
   c. State that discontinuation of participation in the study will involve no loss of benefits to which the patient is entitled.

II. Additional Elements - May be appropriate for some studies

1. State that unforeseeable or unexpected risk(s) may be involved.
2. State that circumstances under which the patient's participation may be terminated by the investigator without the patient's consent.
3. State that additional costs may be incurred by the patient's participation in the study.
4. State the consequences of the patient's decision to withdraw from the study.
5. State that significant new findings that relate to the patient's treatment will be discussed with the patient.
6. State the approximate number of patients involved in the study.

III. Suggested Elements

1. State that a copy of the informed consent form shall be given to the patient.
2. The form should be written in layman's terms.
3. Reference to approval by the IRB, NCI or Cooperative Group may be misleading to the patient.

The sample consent form provided in section 18.0 includes all the required elements as well as the "additional" and "suggested" elements relevant to this study. REBs must consider the sample consent as the basis for review, as this form has been approved by the U.S. National Institutes of Health. Significant changes of wording or deletions of the toxicity or alternative therapy sections of the sample consent must be justified by the REB in writing; note however that additions to these sections are rarely a problem.

Consent Process/ Patient Eligibility

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

16.7 Centre Performance Monitoring

Ineligibility and timeliness are monitored for all centres and the results are reported in the Centre Performance Index. There are minimum standards for performance.

Forms are to be submitted according to the schedule in Appendix IV (Documentation for Study).

16.8 On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring may be conducted at active participating centres at least once every three years in the course of the study, as mandated by U.S. regulations. The auditors will require access to patient medical records to verify the data.

16.8.1 *Regulatory and Monitoring for CTSU Investigators*

Study Audit

To assure compliance with Federal regulatory requirements (CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46) and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

16.9 Case Report Forms

A list of forms to be submitted as well as expectation dates are to be found in Appendix IV.

16.10 Data Submission, SWOG Investigators

Group Members, Affiliates, CCOPs and UCOPs must submit one copy of all data forms at the required intervals directly to the National Cancer Institute of Canada, Clinical Trials Group at the address below:

National Cancer Institute of Canada, Clinical Trials Group
Queen's University
10 Stuart Street
Kingston, Ontario, K7L 3N6

Include the NCIC CTG protocol number and patient serial number as well as the Southwest Oncology Group study number and patient number.

16.11 Data Submission, CTSU Investigators

All forms and documents associated with this study may be downloaded from the NCIC CTG JPR.7 webpage located on the CTSU registered member Web site (http://members.ctsu.org). CTSU investigators should use the protocol-specific NCIC CTG forms and adhere to the NCIC CTG schedule for data submission.

Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the NCIC Clinical Trials Group. Original CRFs should be sent to the NCIC Clinical Trials Group at the address listed in the Contacts Table.

The NCIC Clinical Trials Group will send query notices and delinquency reports directly to the site for reconciliation. Please mail query responses and delinquent data to the NCIC Clinical Trials Group and do not copy the CTSU Data Operations

Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the NCIC Clinical Trials Group.

16.12 Data Submission, UK Investigators

The ICR-CTSU will supply all case report forms (CRFs) and quality of life (QOL) questionnaires to each UK centre. Investigators will submit all completed forms (CRFs and QOL questionnaires) and supporting documentation (i.e. pathology reports, operative reports, chest X-ray reports, and bone scan reports). Investigators will retain one copy of all forms and supporting documentation, and mail two copies to the ICR-CTSU as soon as possible:

Rosa Lau, Data Manager
The Institute of Cancer Research
Section of Clinical Trials
Clinical Trials and Statistics Unit (ICR-CTSU)
Sir Richard Doll Building
Cotswold Road
Sutton, Surrey SM2 5NG, UK

Tel: 020 8722 4152 / Fax: 020 8770 7876

The ICR-CTSU will keep a log of randomized patients and all returned forms and documentation. The ICR will then mail one copy (original)of all returned forms and documentation to the NCIC CTG on a regular basis (monthly or two-weekly depending on the number of patients). ICR-CTSU will retain one copy of all CRFs. It is important that all forms and supporting documentation are submitted from investigators to ensure internal validation, auditing, and quality assurance that may take place at the NCIC CTG. All data entry, queries, and data analysis will be conducted in the central office at the NCIC CTG. The NCIC CTG will send queries to the ICR-CTSU who will forward them to centres. Replies to queries will be sent back to the ICR-CTSU who will forward them to the NCIC CTG.

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REVISED: 98-DEC-15; AMENDED: 99-JUN-04; 00-JUL-18; 02-FEB-25; AMENDMENT #7: 2008-JUN-13

APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Prestudy	Prior to Hormone Resistance	At the time of Hormone Resistance	After Hormone Resistance Required Annually
Physical				
History	2 wks prior to randomization (14 days)			
Physical Exam				
Rectal Exam				
Performance Status		q 4 months	x	x
Haematology				
Hemoglobin	1 mth prior to randomization (28 days)	Annually	x	x
WBC and differential				
Platelets				
Biochemistry				
Serum PSA	1 mth(28 d) prior to randomization	q 2 mths	x	x
Serum testosterone			x	
Serum Creatinine	1 mth(28 d) prior to randomization			
Bilirubin, Alkaline Phosphatase, LDH / AST / ALT	1 mth(28 d) prior to randomization	IAS Arm: q monthly x 4 of each 8 month treatment cycle CAD Arm: q monthly x 4 then q 6 months		
Fasting Serum cholesterol total/HDL/LDL	1 mth(28 d) prior to randomization	Annually	x	x
Radiology				
Chest x-ray	8 weeks (56 days) prior to randomization			
Bone Scan	8 weeks (56 days) prior to randomization	Annually		
Toxicity	2 wks prior to randomization (14 days)	IAS Arm: q 4 mths & end of each on-treatment cycle CAD Arm: q 4 mths		x
Quality of Life				
EORTC QLQ-C30 + trial specific questionnaire	2 wks prior to randomization (14 days)	q 4 mths for 2 years then q 8 mths until hormone resistance	x	x
Other Investigations				
Translational Research Blood Sample-Sect.13.0 (NCIC CTG centres only)	prior to treatment	CAD Arm: Annually for 5 yrs IAS: not required	IAS Arm only	CAD Arm: Annually for 5 years from randomization
Additional Blood Sample for RT-PCR testing (Toronto centres only)	prior to treatment	CAD Arm: Annually for 5 years IAS Arm: Beginning and end of each non-treatment interval		CAD Arm: Annually for 5 years from randomization
Nutrition Survey (NCIC CTG centres only)	prior to treatment			

APPENDIX II - PERFORMANCE STATUS (ECOG)

Grade

0 Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work) (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20)

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

All drugs are commercially available.

Please refer to section 3.0.

REVISED: 98-DEC-15; AMENDED: 99-JUN-04; AMENDED: 02-FEB-25; AMENDMENT #7: 2008-JUN-13

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

Form	To be Completed	Due in Central Office	Supporting Documentation Required
Eligibility Checklist/Form 1 Initial Evaluation	prior to calling to randomize the patient	within 10 wks of randomization	• signed copy of patient consent form • operative report(s) • pathology report(s) • chest x-ray report(s) • bone scan report(s) • baseline quality of life questionnaire • Nutrition Survey
Form 3 Systemic Therapy/Adverse Event Report	every 8 months prior to hormone resistance	within 8 wks of date of attendance	• quality of life questionnaire • copies of radiology/pathology reports
Form 5 Follow-up Report	Every 8 months prior to hormone resistance for patient who have permanently discontinued protocol therapy for any reason	Within 8 wks of date of attendance	• copies of radiology/pathology reports
Form 5S - Short Follow-up Report	annually from randomization after hormone resistance	within 12 wks of the date of attendance	• copies of radiology/pathology reports
Form 5M* Minimal Follow-up	annually from randomization	within 12 wks of the date of attendance	
Off Treatment Report	At the time patient permanently discontinues Protocol therapy for any reason	Within 8 wks of off treatment date	
Form 6 Final Report	at the time of the patient's death	within 8 wks of the patient's death	• autopsy report if done • death report if Cause of death other than prostate cancer
Form 9 Hormone Resistance Report	at the first evidence of meeting criteria of hormone resistance	within 8 wks of the event	• quality of life questionnaire
Serious Adverse Event Report Form**	at the time of the event	NCIC CTG centres: 10 days SWOG centres: 3 days CTSU centres: 3 days UK centres: 3 days	
Quality of Life	by the patient • within 2 wks prior to randomization, • every 4 months for the first 2 years, • then every 8 months until completion of protocol therapy, • at the time of hormone resistance • annually from randomization after hormone resistance		
Nutrition Survey (Canadian centres only)	by the patient prior to start of treatment		

* For ineligible patients and for all patients after the trial is closed and published.
** See section 11.0 Adverse Event Reporting for details.

APPENDIX V - COMMON TOXICITY CRITERIA VERSION 2.0

This study will utilize the Common Toxicity Criteria Version 2.0 for toxicity and adverse event reporting. A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov/). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

The NCIC CTG central office will provide this document to NCIC CTG centres.

The ICR-CTSU will provide this document if required to UK centres.

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and toxicity data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble
   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed please document the reason(s) on the appropriate case report form.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, eg: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some

trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

   Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if he is willing to complete one:

   If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

   If this is not feasible, then ask the patient if he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make note on the questionnaire that the questionnaire was completed over the phone.

   If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

   Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

   Should the patient not wish to answer the questionnaire in the clinic but insist on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply,

the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

   If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

This box to be completed by the clinical research associate:	NCIC CTG Patient Serial #: _____ Intergroup Patient Serial #: _____	Patient. Initials: ___ ___ ___

REVISED: 98-DEC-15

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (PR.7)

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best single response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

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

EORTC QLQ-C30 (Core 30 Questionnaire © copyright 1992 EORTC Study Group on Quality of Life. All rights reserved.)

This box to be completed by the clinical research associate:	NCIC CTG Patient Serial #: _____ Intergroup Patient Serial #: _____	Patient. Initials: ___ ___ ___

REVISED: 98-DEC-15

During the past week:	Not at All	A Little	Quite a Bit	Very Much
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
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

Please go on to the next page

REVISED: 98-DEC-15

During the past week:	Not at All	A Little	Quite a Bit	Very Much
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

REVISED: 98-DEC-15

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have to pass urine more frequently than normal for you?	1	2	3	4
32. Did you have difficulty passing your urine?	1	2	3	4
33. Did you have pain when you passed urine?	1	2	3	4
34. Did you have difficulty controlling your urination (for example, dribbling)?	1	2	3	4
35. Did you have to get up at night to pass urine? (If you answered "not at all" go to question 37. If you answered "a little", "quite a bit" or "very much" go to question 36.)	1	2	3	4
36. How much did getting up at night interfere with your sleep?	1	2	3	4
37. Did you have urgency to move your bowels?	1	2	3	4
38. Did you have pain or discomfort with bowel movements?	1	2	3	4
39. Did you have bothersome hot flashes?	1	2	3	4
40. Did you have bothersome breast swelling?	1	2	3	4
41. Did you have bothersome breast tenderness?	1	2	3	4
42. Did you have desire for sexual activity?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate:	NCIC CTG Patient Serial #: _____ Intergroup Patient Serial #: _____	Patient. Initials: ___ ___ ___

REVISED: 98-DEC-15

During the past week:	Not at All	A Little	Quite a Bit	Very Much
43. Did you have any erections? (If you answered "not at all" go to question 47. If you answered "a little", "quite a bit" or "very much" go to question 44.)	1	2	3	4
44. Have you been able to keep an erection? (If you answered "not at all" go to question 47. If you answered "a little", "quite a bit" or "very much" go to question 45.)	1	2	3	4
45. Have you been sexually active? (If you answered "not at all" go to question 47. If you answered "a little", "quite a bit" or "very much" go to question 46.)	1	2	3	4
46. Did you feel satisfied after sexual activity?	1	2	3	4
47. Did you get emotional support from your family?	1	2	3	4
48. Did family communication about your illness bother you?	1	2	3	4
49. Did you have concerns about communication with your medical caregiver(s)?	1	2	3	4
50. To what extent has your medical treatment concerned you?	1	2	3	4
51. Did you feel in control of your life?	1	2	3	4
52. Did you feel that you had accepted your illness?	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

This box to be completed by the clinical research associate:	NCIC CTG Patient Serial #: _____ Intergroup Patient Serial #: _____	Patient. Initials: ___ ___ ___

REVISED: 98-DEC-15

This box to be completed by the clinical research associate

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

During treatment:

☐ 4 months ☐ 8 months ☐ 12 months ☐ 16 months ☐ 20 months ☐ 24 months

☐ 32 months ☐ 40 months ☐ 48 months ☐ 56 months ☐ 64 months ☐ 72 months ☐ _____

☐ at Hormone Resistance

After Treatment (annually until death): ☐ _____month from randomization

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed? ☐ home ☐ clinic ☐ another centre

Comments:

_____

_____

_____

_____

_____

NCIC CTG use only

Logged: _____	Study Coord: _____	RA: _____	Data Ent'd:	Verif:
___ - ___ - ___	___ - ___ - ___	___ - ___ - ___	_____	_____

(96-01-12)

NCIC CTG Trial PR.7

A PHASE III RANDOMIZED TRIAL COMPARING INTERMITTENT VERSUS CONTINUOUS ANDROGEN SUPPRESSION FOR PATIENTS WITH PROSTATE-SPECIFIC-ANTIGEN PROGRESSION IN THE CLINICAL ABSENCE OF DISTANT METASTASES FOLLOWING RADIOTHERAPY FOR PROSTATE CANCER

Nutrition Survey

Instructions:	This cover sheet is to be completed by clinical research associate/investigator. This cover sheet must be completed for all patients whether the nutrition survey is completed or not by the patient. Attach the completed cover sheet to the nutrition survey when returned by the patient. Please check that all questions have been answered and no question has more than one answer.
Note:	If the entire nutrition survey is not completed, please complete and return this cover page with the case report form.

NCIC CTG Patient Serial No.: _____ Patient Hospital No.: _____Patient Initials:_____ _____ _____
(first, middle, last)

Institution: _____ Investigator: _____

The Nutrition Survey is required by all Canadian patients prior to initiation of androgen ablation.

Was nutrition survey completed?

___ Yes →→→ Date nutrition survey completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If no, reason: _____

Where was nutrition survey completed? ☐ home ☐ clinic ☐ another centre

___ No →→→ Please fill in today's date: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

Specify reason nutrition survey not completed (check one):

___ 1. Patient kept appointment for examination, but could not complete nutrition survey due to illness.

___ 2. Patient kept appointment for examination, but refused to complete nutrition survey for reason other than illness.

Specify reason: _____

___ 3. Patient did not keep appointment. Specify reason: _____

___ 4. Patient could not be contacted.

___ 5. Nutrition survey not administered due to institution error.

___ 6. Other reason, specify: _____

NCIC CTG use only

Logged: _____	Study Coord: _____	RA: _____	Data Ent'd:	Verif:
_____ - ____ - ___	_____ - ____ - ___	_____ - ____ - ___	_____	_____

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

A Phase III Randomized Trial Comparing Intermittent versus Continuous Androgen Suppression for Patients with Prostate-Specific-Antigen Progression in the Clinical Absence of Distant Metastases following Radiotherapy for Prostate Cancer

NCIC CTG - PR.7

NUTRITION SURVEY

A person's health can be affected by the kinds and amounts of food they eat and the beverages they drink. Please complete the chart on the next pages including foods and beverages consumed both at home and away from home.

For every food or beverage mark "YES" or "NO" → if "YES" -- indicate the number of times per day, week or month and mark one of the serving sizes.

Here are some examples showing how to complete the chart.

EXAMPLES:

A: *Hank drinks whole milk once a day - about 1½ cups each time …*

This is how he would show that on the chart:

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Whole milk or homo and beverages made with it	☑ Yes → ☐ No	1 ☑ Day ☐ Week ☐ Month	☐ 1 cup	☑ More than 1 cup	☐ Less than 1 cup

B: *Hank eats dark rye in a sandwich for lunch five times a week, two slices each time …*

he would record his bread this way:

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Dark rye, pumpernickel, fibre-enriched bread and rolls	☑ Yes → ☐ No	5 ☐ Day ☑ Week ☐ Month	☑ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices

C: *Hank only eats roast beef or steak every 3 or 4 months …*

he would show that on the food chart like this:

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Roast beef and steak	☐ Yes → ☑ No	___ ☐ Day ☐ Week ☐ Month	☐ 4 ounces	☐ More than 4 ounces	☐ Less than 4 ounces

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

NUTRITION

1. White or Chocolate Milk to drink

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
2% milk and beverages made with it	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Whole milk or Homo and beverages made with it	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Skim milk and beverages made with it	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Milkshakes	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ Small	☐ Regular	☐ Large

2. Cheese, Yogurt and Eggs

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Hard cheese such as cheddar	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 inch cube	☐ More than 1 inch cube	☐ Less than 1 inch cube
Processed cheese slices (including those on sandwiches and hamburgers)	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 slice	☐ 2 slices	☐ More than 2 slices
Cottage cheese	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Any other cheese and cheese spreads	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 inch cube/ 1 tbsp	☐ More than cube/tbsp	☐ Less than cube/tbsp
Yogurt	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ Small carton	☐ Large carton	☐ ½ cup
Eggs	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 egg	☐ 2 eggs	☐ 3 or more eggs

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

3. Breakfast Cereals

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Oatmeal porridges, oat bran	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ¾ cup	☐ More than ¾ cup	☐ Less than ¾ cup
All bran 100% Bran, Fibre-One, Fibre Plus	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ¾ cup	☐ More than ¾ cup	☐ Less than ¾ cup
Bran Flakes, Corn Bran, Muffets, Shredded Wheat	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ¾ cup	☐ More than ¾ cup	☐ Less than ¾ cup
Any other cooked or dry cereal such as Corn Flakes, Rice Krispies, Malto-O-Meal	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ¾ cup	☐ More than ¾ cup	☐ Less than ¾ cup

If you eat cereal, do you usually add sugar? ☐ Yes ☐ No

Which ONE of the following do you use most often on your cereal?
☐ cream/half & half
☐ whole milk
☐ 2% milk
☐ skim milk

4. Breads, Rolls and Muffins

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Whole wheat or light rye bread and rolls	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
Dark rye, pumpernickel, fibre-enriched bread and rolls	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
White, Italian, French, egg, raisin bread and rolls	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
Bran or corn muffins	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 muffin	☐ 2 muffins	☐ 3 or more muffins
Any other muffin such as blueberry, plain chocolate chip	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 muffin	☐ 2 muffins	☐ 3 or more muffins

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

If you eat bread, do you add:

	Always	Usually	Sometimes	Rarely/Never
Butter, margarine or cream cheese	☐	☐	☐	☐
Mayonnaise or salad dressing	☐	☐	☐	☐
Peanut butter	☐	☐	☐	☐
Jelly, jam, honey or other sweet spread	☐	☐	☐	☐

If you eat muffins, do you add:

	Always	Usually	Sometimes	Rarely/Never
Butter, margarine or cream cheese	☐	☐	☐	☐
Mayonnaise or salad dressing	☐	☐	☐	☐
Peanut butter	☐	☐	☐	☐
Jelly, jam, honey or other sweet spread	☐	☐	☐	☐

5. *Meat, Poultry and Fish*

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Roast beef and steak	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 4 ounces	☐ More than 4 ounces	☐ Less than 4 ounces
Roast pork and pork chops	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 4 ounces	☐ More than 4 ounces	☐ Less than 4 ounces
Liver, any type	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 4 ounces	☐ More than 4 ounces	☐ Less than 4 ounces
Fried chicken, nuggets, chicken sandwiches	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 2 pieces 6 nuggets 1 sandwich	☐ 4 pieces 9 nuggets 2 sandwich	☐ More than 4 pieces 9 nuggets
Barbecued chicken	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ quarter chicken	☐ half chicken	☐ 2 pieces or slices
Any other chicken, turkey or other poultry	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
Fried fish, fried fish sandwiches	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 piece / sandwich	☐ 2 pieces / sandwiches	☐ 3 or more pieces / sandwiches
Any other fish, canned, fresh or frozen, such as tuna	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 piece/ ¼ cup	☐ 2 pieces/ ½ cup	☐ 3 or more pieces or ¾ cup

… continued

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

5. *Meat, Poultry and Fish continued*

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Hamburgers and cheeseburgers	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ single patty	☐ double patty	☐ more than 3 single or 2 dbl patties
Weiners, hot dogs	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ regular	☐ large/ 2 regular	☐ more than 1 lg/2 reg
Bacon	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
Sausage	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 links	☐ 3-4 links	☐ 1-2 large sausages
Cold-cuts, luncheon meats such as bologna, salami, chicken loaf or ham	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices

	Always	Usually	Sometimes	Rarely/Never
If you eat meat or chicken, do you add gravy?	☐	☐	☐	☐
If you eat meat, do you eat the fat?	☐	☐	☐	☐
If you eat chicken, do you eat the skin?	☐	☐	☐	☐
If you eat fish, do you have tartar sauce or mayonnaise with it?	☐	☐	☐	☐

6. *Mixed meat, fish or chicken dishes*

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Meat and chicken pies	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 slice/ small pie	☐ 2 slices/ small pies	☐ 3 or more sm pies/ slices
Meat and fish stews	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Spaghetti, lasagna, other pasta with meat tomato sauce	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 2 cups	☐ More than 2 cups	☐ Less than 2 cups

… continued

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

6. *Mixed meat, fish or chicken dishes continued*

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Macaroni and cheese, other pasta dishes with cheese	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 2 cups	☐ More than 2 cups	☐ Less than 2 cups
Pizza	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-2 slices	☐ 3-4 slices	☐ 5 or more slices
Any other mixed dishes, made with ground meat, fish or chicken	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Any other pasta, or noodles	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Rice any type	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup

7. *Vegetables*

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
French fries, home fries, pan fried potatoes	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ small fries	☐ large fries	☐ 1 cup
Any other potatoes, baked, boiled, salad	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ more than 1 cup	☐ Less than 1 cup
Broccoli	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Carrots, raw and cooked	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Corn	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup small cob	☐ More than ½ cup	☐ Less than ½ cup
Green peas	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup

… continued

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

7. Vegetables continued

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Green beans, string beans, yellow beans	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Any other beans, peas, lentils, lima, navy, baked, pork and beans	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Squash all types	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Salad – combination lettuce and tomato	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Any other salads such as coleslaw, carrot, bean, spinach	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ More than 1 cup	☐ Less than 1 cup
Any other vegetables such as cabbage, brussel sprouts	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup

	Always	Usually	Sometimes	Rarely/Never
If you eat potatoes or rice, do you add butter, margarine, gravy or sour cream?	☐	☐	☐	☐
If you eat vegetables, do you add butter, margarine, cheese or other sauce?	☐	☐	☐	☐
If you eat salads, do you add diet, low-fat, low-calorie dressings or mayonnaise?	☐	☐	☐	☐
If you eat salads, do you add regular mayonnaise, salad dressing, or salad oil?	☐	☐	☐	☐

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

8. Fruit

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Apples, applesauce	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 apple/ ½ cup	☐ 2 apples/ 1 cup	☐ More than 2 apples/ 2 cups
Bananas	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 banana	☐ 2 bananas	☐ 3 or more bananas
Oranges, nectarines	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 orange/ nectarine	☐ 2 oranges/ nectarines	☐ 3 or more oranges/ nectarines
Pears, peaches fresh or canned	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 fruit/ ½ cup	☐ 2 fruit/ 1 cup	☐ More than 2 fruit/ 2 cups
Raisins, prunes, other dried fruit	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ 1 cup	☐ More than 1 cup
Any other fruit, including berries and fruit cocktail and salad	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 fruit/ ½ cup	☐ 2 fruit/ 1 cup	☐ More than 2 fruit/ 2 cups

9. Beverages

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Orange juice	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ 1 cup	☐ More than 1 cup
Apple, other citrus juices	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ 1 cup	☐ More than 1 cup
Tomato, mixed vegetable juices	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ 1 cup	☐ More than 1 cup
Fruit drinks such as Tang or Kool-Aid	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ 1 cup	☐ More than 1 cup

… continued

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

9. Beverages continued

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Regular soft drinks, not diet	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ small/ 1 can	☐ medium	☐ large
Coffee	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ 2 cups	☐ 3 or more cups
Tea	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 cup	☐ 2 cups	☐ 3 or more cups

If you drink coffee:

do you add sugar? ☐ Yes ☐ No

Which one of the following do you use most often?
- ☐ No milk or cream
- ☐ Whole milk or evaporated 2% milk
- ☐ Cream or evaporated whole milk
- ☐ 2% milk
- ☐ Skim milk

If you drink tea:

do you add sugar? ☐ Yes ☐ No

Which one of the following do you use most often?
- ☐ No milk or cream
- ☐ Whole milk or evaporated 2% milk
- ☐ Cream or evaporated whole milk
- ☐ 2% milk
- ☐ Skim milk

10. Desserts and Snacks

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Ice cream, ice milk, sherbet	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 scoop	☐ 2 scoops	☐ 3 or more scoops
Cake	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 slice	☐ 2 slices	☐ 3 or more slices
Pie	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1 slice	☐ 2 slices	☐ 3 or more slices

… continued

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

10. Desserts and Snacks continued

	Do you have this food or beverage at least once a month?	About how many times per day or week or month?	About how much do you have each time?		
Cookies, crackers	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1-5	☐ 5-10	☐ More than 10
Donut, danish, croissant	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 1	☐ 2	☐ 3 or more
Potato chips	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ small bag	☐ More than small bag	☐ Less than small bag
Popcorn	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 2 cups	☐ More than 2 cups	☐ Less than 2 cups
Peanuts, other nuts/seeds	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ ½ cup	☐ More than ½ cup	☐ Less than ½ cup
Chocolate	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ regular bar	☐ large bar	☐ 2 pieces

11. Calcium supplements	☐ Yes → ☐ No	___ ☐ Day ☐ Week ☐ Month	☐ 50-300 mg	☐ 301-900 mg	☐ more than 900 mg

12. Smoking Alcohol

How much do you currently smoke daily? ☐ none
☐ less than ½ pack
☐ more than ½ pack

How many alcoholic beverages do you consume in a week? ☐ none
☐ less than 5
☐ between 6 - 10
☐ more than 10

13. Surgery

Have you had a vasectomy? ☐ No
☐ Yes → If yes, what year? _____

This box to be completed by the clinical research associate

NCIC CTG Patient Serial No. _____ Patient Hospital No. _____ Patient Initials: ____ ____ ___

PHYSICAL ACTIVITIES

1. Which of the following sentences best describes your usual daily activities or work habits?
   - ☐ I am usually sitting during the day and do not walk about very much.
   - ☐ I stand or walk about quite a lot during the day but I do not have to carry or lift things very often.
   - ☐ I usually lift or carry light loads, I have to climb stairs or hills often.
   - ☐ I do heavy work or carry very heavy loads.

2. How likely do you think it is that your current level of physical activity will lead to health problems for you?
   - ☐ Very likely
   - ☐ Somewhat likely
   - ☐ Somewhat unlikely
   - ☐ Very unlikely

3. How many of your friends take part in regular physical exercise?
   - ☐ All of them
   - ☐ Most of them
   - ☐ About half of them
   - ☐ A few of them
   - ☐ None of them

4. How long ago did you last have your blood pressure checked?
   - ☐ Within the last 6 months
   - ☐ 6 months to one year ago
   - ☐ 13 months to 2 years ago
   - ☐ More than 2 years ago
   - ☐ Never had it checked
   - ☐ Don't know

5. Do you think that you could improve your health by changing your eating habits?
   - ☐ Yes
   - ☐ No
   - ☐ Don't know

HEIGHT & WEIGHT

1. What is your height? _____ cm or _____ ft. _____ ins.
2. What is your weight? _____ kg. or _____ lbs
3. What would you like to weigh? _____ kg. or _____ lbs.

Please check to see that you have answered all the questions

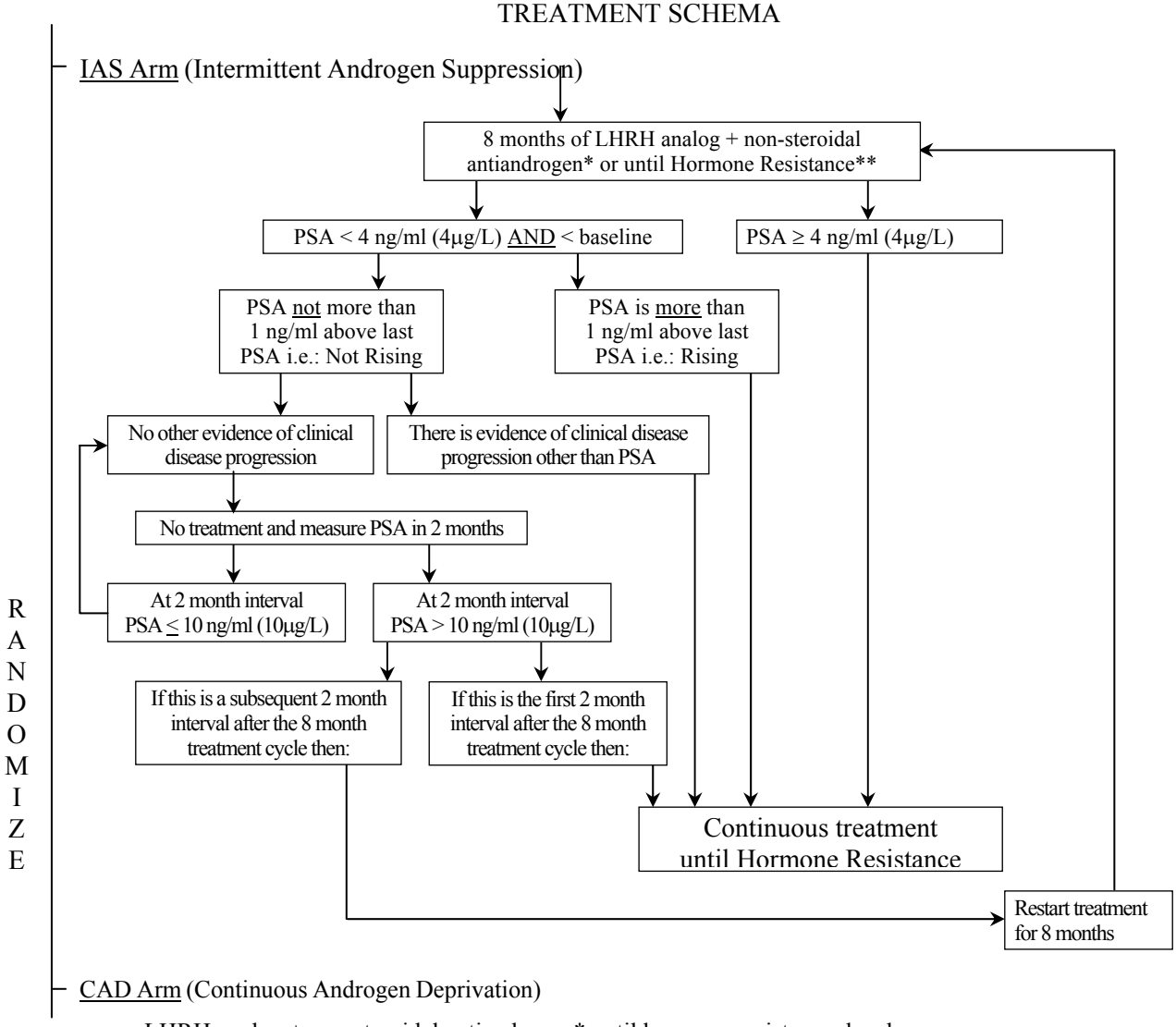
Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VIII – PREVIOUS SCHEMA

TREATMENT SCHEMA



LHRH analog + non-steroidal antiandrogen* until hormone resistance develops.
OR
orchiectomy +/- non-steroidal antiandrogen* (optional) until hormone-resistance develops.

Planned Sample Size: 1340 patients

NCIC CTG centres to use:
LHRH analog - buserelin
Antiandrogen - nilutamide*

SWOG/CTSU centres to use:
LHRH analog - goserelin or leuprolide
Antiandrogen - nilutamide or flutamide or bicalutamide*

UK centres to use:
LHRH analog - goserelin or leuprorelin
Antiandrogen - flutamide or bicalutamide or cyproterone acetate*

* For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician.

** Hormone resistance criteria can only be met while the patient is receiving treatment. During an off-treatment interval please follow the algorithm.

APPENDIX IX - HORMONE TREATMENT OPTIONS

Permitted Antiandrogen Therapy **

Drug	Unit Size	Dose	Route	Schedule
Nilutamide**	50 mg tablets	300 mg/day first month then 150 mg/day	Orally	once daily
Flutamide**	125 mg	750 mg/day	Orally	3 divided doses per day
	250 mg	750 mg/day		
Bicalutamide** (US and UK centres)	50 mg	50 mg/day	Orally	once daily
Cyproterone Acetate** (UK centres)	100 mg	300 mg/day	Orally	3 divided doses per day

** For safety reasons the antiandrogen must be given for a minimum of 4 weeks to block tumour flare at each on-treatment interval. Continuation of the antiandrogen beyond flare is optional at the discretion of the treating physician. It is recommended that patients declared off study but restarting LHRH analog should also begin with a minimum of 4 weeks of antiandrogen to prevent tumor flare; continuation after flare period is always optional.

Permitted LHRH Analog Therapy* (or Bilateral Orchiectomy)

Drug	Dose	Route	Schedule**
Buserelin (Suprefact Depot®)	6.3 mg	Subcutaneous implant	every 2 months
	9.45 mg		every 3 months
Goserelin (Zoladex®)	3.6 mg	Subcutaneous implant	every month
	10.8 mg		every 3 months
Leuprolide as Eligard®	7.5 mg	Subcutaneous injection	every month
	22.5 mg		every 3 months
	30 mg		every 4 months
	45 mg		every 6 months
Leuprolide as Lupron Depot®	7.5 mg	Intramuscular injection	every month
	22.5 mg		every 3 months
	30 mg		every 4 months
Leuprorelin (Prostap®)	3.75 mg	Intramuscular or subcutaneous injection	every month
	11.25 mg	Subcutaneous injection	every 3 months

* For patients randomized to IAS arm any combination of injections or insertions to equal 8 month course may be used.

** UK Centres - Patients randomized to the IAS arm must receive the monthly preparation of LHRH analog. Patients must not receive the three monthly preparation of LHRH analog if on the IAS arm.

APPENDIX X - CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	Original CRFs to be mailed to: NCIC Clinical Trials Group Queen's University 10 Stuart Street Kingston, Ontario, K7L 3N6 Canada Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility questions, contact the Study Coordinator at the NCIC Clinical Trials Group at 1-613-533-6430.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org		

APPENDIX XI – ICR-CTSU ADDRESS AND CONTACT INFORMATION

Randomization	Serious Adverse Event Reporting	Forms & Documentation Submission
Monday – Friday 09h00 – 17h00 Tel 020 8643 7150 Fax 020 8722 4368		Rosa Lau, Data Manager The Institute of Cancer Research Section of Clinical Trials Clinical Trials and Statistics Unit (ICR-CTSU) Sir Richard Doll Building Cotswold Road Sutton, Surrey SM2 5NG, UK Tel: 020 8722 4152 Fax: 020 8770 7876

UK Chief Investigator	ICR-CTSU Clinical Trials Unit	
Dr. David Dearnaley, Study Chair Academic Unit of Radiotherapy Royal Marsden Hospital Downs Road Sutton SM2 5PT Tel: 020 8661 3271 Fax: 020 8643 8809 Email: David.Dearnaley@icr.ac.uk	Dr. Emma Hall Deputy Head, CTSU (ICR-CTSU) Section of Clinical Trials Brookes Lawley Building Institute of Cancer Research Cotswold Road Sutton, Surrey SM2 5NG Tel: 020 8722 4292 Fax: 020 8770 7876 Email: Emma.Hall@icr.ac.uk	Rosa Lau, Data Manager The Institute of Cancer Research Section of Clinical Trials Clinical Trials and Statistics Unit (ICR-CTSU) Sir Richard Doll Building Cotswold Road Sutton, Surrey SM2 5NG, UK Tel: 020 8722 4152 Fax: 020 8770 7876 Email: rosa.lau@icr.ac.uk

APPENDIX XII - SAMPLE CONSENT FORM

ENGLISH Sample Consent Form

A PHASE III RANDOMIZED TRIAL COMPARING INTERMITTENT VERSUS CONTINUOUS ANDROGEN SUPPRESSION FOR PATIENTS WITH PROSTATE-SPECIFIC-ANTIGEN PROGRESSION IN THE CLINICAL ABSENCE OF DISTANT METASTASES FOLLOWING RADIOTHERAPY FOR PROSTATE CANCER

Le formulaire de consentement est disponible en français sur demande

Background

I have been asked to participate in a research study because I have prostate cancer which has come back after treatment.

Prostate cancer generally requires male hormone in order to grow. Most male hormone comes from the testicles in the form of testosterone. The adrenal glands also produce a small amount of male hormone. Standard treatment in a situation like mine involves removal or blocking of the body's male hormone, and is therefore referred to as "hormone treatment". This could be accomplished by either surgery to remove the testicles, injections every 1-4 months (4-16 weeks) to block the production of testosterone, tablets taken daily by mouth, or a combination of these.

Purpose and Design of Study

Although hormone treatment is usually very successful in causing the cancer to shrink and in decreasing the PSA (Prostate Specific Antigen, which indicates the activity of the cancer), the effect does not last forever and eventually the cancer starts to progress despite continued hormone treatment. This may occur within a few months of starting the hormone treatment, or may not happen for several years. When this happens, it is called "hormone resistance" and the cancer can then be difficult to control.

Some preliminary studies have been done using hormone treatment in cycles or "intermittently" for men in a situation like mine with recurrent prostate cancer. These studies show that men treated with intermittent hormone therapy do not seem to do any worse than expected, and may benefit in terms of quality of life.

The effect of intermittent therapy on the development of hormone-resistance in patients is unknown. It could have a bad effect on cancer progression by making an unstable hormonal environment. Alternatively, animal studies suggest it may delay the onset of hormone resistance by intermittently letting the body's normal male hormone balance return. Based on studies to date, it is likely that, if there is an adverse effect, it is relatively small.

This research study will compare continuous hormone treatment to intermittent hormone treatment to determine if intermittent treatment is as effective and if it improves quality of life. At this time, no one knows which treatment may be better for me.

If I agree to participate in this study I will be "randomized" (a process of selection similar to flipping a coin) to receive either standard continuous hormone treatment or intermittent hormone therapy.

I will be participating in this study until there is evidence that my disease has stopped responding to the treatment (hormone resistance). However, even after I am finished participating in this study, information will still be collected about my progress for the rest of my life.

Approximately 1340 patients are expected to be involved in this study.

Description of Treatment

Because there are a number of similar drugs that may be used in this study I understand that I am able to discuss the treatment schedules planned for me with my doctor.

Arm 1: Intermittent Treatment

If I am randomized to receive intermittent treatment, I will be prescribed pills to be taken every day for a minimum of 4 weeks plus regular injections or implants placed just beneath the skin, which, depending on the actual drug used can be every month, or every two months, or every three months, or every four months. At each visit up to 1 tablespoon of blood will be taken for PSA and other blood tests. If my PSA falls to normal during an 8 month treatment period, I would be able to stop these medications for a period of time generally ranging from 3 to 12 months or more. The exact length of time will depend on the changes in my PSA level. During the period of non-treatment I will be carefully monitored with blood tests every 2 months to detect the earliest PSA change. When my PSA level meets the planned requirement, I will restart the hormonal treatment, exactly as it had been given previously, for another 8 month period. It is likely that I will go through several cycles of hormone treatment with "no treatment" intervals in between. If my PSA is not well controlled or I develop evidence of new disease I may begin continuous treatment similar to Arm 2.

If I was sexually active before starting hormone treatment, there is a 75% chance that sexual function may return within a few weeks of stopping the hormone treatment.

Arm 2: Standard Treatment

If I am randomized to this treatment arm, my hormone treatment will be given continuously without scheduled interruptions. This will consist of either regular injections or implants

placed just beneath the skin, which, depending on the actual drug used can be every month, or every two months, or every three months, or every four months, or surgical removal of the testicles, plus or minus pills taken daily. The pills must be taken for a minimum of 4 weeks. At each visit up to 1 tablespoon of blood will be taken for PSA and other blood tests.

Side Effects

While on the study, you are at risk for the side effects listed below. You should discuss these with your doctor. As with any experimental treatment combination, additional unexpected and sometimes serious side effects are a possibility.

Because the effects the treatment may have on a fetus are unknown, you should not father a baby while on this study. An effective method of birth control should be used while you are on study treatment.

Your doctor will watch you closely to see if you have side effects. When possible, other drugs will be given to you to make side effects less serious and uncomfortable. Many side effects go away shortly after treatment is stopped but in some cases side effects can be serious, long-lasting or permanent.

The drugs you may receive will be hormone agents, one anti-androgen and one luteinizing hormone releasing hormone (LHRH) agonist. These drugs act on prostate cancer by interfering with the actions of male hormones on prostate cancer cells. There are several anti-androgen and LHRH hormone agents available to treat prostate cancer and your doctor will tell you which one you will receive. In general, these drugs cause side effects related to the suppression of the effects of the male hormones. Your doctor will inform you of the particular side effects of the hormone agents you will be prescribed.

Risks and side effects shared by ANTI-ANDROGEN agents (Bicalutamide, Flutamide, Nilutamide, Cyproterone (Androcur)) on this trial include:

Very likely (21% or more):
- hot flashes
- impotence, reduced sexual drive
- nausea, vomiting

Less likely (5 – 20%):
- excessive development of breasts in men, which may include breast tenderness
- changes in blood pressure (hyper or hypotension)
- swelling from excessive accumulation of fluid in tissue
- dizziness
- difficulty sleeping
- rash and itching
- constipation
- diarrhea
- decrease in the part of red blood cells that carry oxygen
- elevated liver function tests which may cause jaundice

Rarely (1 – 4%):
- headache
- drowsiness
- appetite changes
- changes in the blood tests associated with kidney function
- decreased bone marrow function which may reduce number of infection fighting cells
- heart disease including heart failure and heart attack

Additional risks and side effects associated with BICALUTAMIDE that are considered to be *medically important* are:

Less likely (5 – 20%):
- numbness and tingling in hands and feet
- excess sugar in the blood (hyperglycemia)
- flu-like syndrome
- infection
- difficulty breathing
- blood in the urine

Rarely (1 – 4%):
- acute inflammation of the lungs (interstitial lung disease)

Additional risks and side effects associated with FLUTAMIDE that are considered to be *medically important* are:

Rarely (1 – 4%):
- confusion
- blurred vision
- inflammation of the liver which may interfere with liver function
- exposure to light may cause skin reddening, blebs, and skin ulcers (photosensitivity)

Rarely *Breast Cancer* has been associated with Flutamide.

AVOID GRAPEFRUIT AND GRAPEFRUIT JUICE for the duration of treatment with FLUTAMIDE, as they may interact with this agent.

Additional risks and side effects associated with NILUTAMIDE that are considered to be *medically important* are:

Less Likely (5 - 20%):
- photophobia, inability to adapt to a sudden change in lighting

Rarely (1 – 4%):
- breathing problems (shortness of breath, coughing)
- acute inflammation of the lungs (interstitial lung disease)
- pneumonitis (may include cough, shortness of breath, chest pain or fever)
- abdominal pain or tenderness
- flu-like syndrome
- excess sugar in the blood (hyperglycemia)
- intolerance to alcohol

Additional risks and side effects associated with CYPROTERONE that are considered to be *medically important* are:

- fatigue
- weakness
- breathing problems (shortness of breath on effort, coughing)
- blurred vision, photophobia
- depression
- hair loss
- excess sugar in the blood (hyperglycemia)
- liver failure
- scarring of the lungs (pulmonary fibrosis)
- osteoporosis

Risks and side effects shared by two or more of the LHRH agents (Leuprolide, Goserelin, Buserelin) on this trial include:

Very likely (21% or more):
- hot flashes
- impotence, reduced sexual drive
- nausea, vomiting
- pain

Less likely (5 – 20%):
- tiredness
- increased urge to urinate and the need to urinate more often
- decrease in the size of the testicles
- excessive development of breasts in men, which may include breast tenderness
- changes in blood pressure (hypo or hypertension), which has rarely been associated with strokes

- dizziness, which may include room spinning (vertigo)
- difficulty sleeping
- numbness and tingling in hands and feet
- skin redness and irritation at the injection site
- constipation
- difficulty breathing
- lack or loss of strength
- headache
- muscle pain
- joint pain
- bone pain
- changes in serum lipids and proteins
- irregular heartbeat
- appetite changes

Rarely (1 – 4%):
- swelling from excessive accumulation of fluid in tissue
- itchy rash
- diarrhea
- weight gain or loss
- elevated liver function tests
- cough
- disease flare reaction (increased bone pain, urinary tract obstruction, and spinal cord compression which can cause pain, tingling in the arms and legs, and problems with movement and sensation, rarely including paralysis)
- heart disease including failure and heart attack
- benign tumour of the pituitary gland (pituitary adenoma)
- fever
- visual changes
- loss of memory
- allergic reaction, in severe cases can include anaphylactic shock (characterized by severe low blood pressure, poor blood flow to tissues and difficulty breathing)

Additional risks and side effects associated with LEUPROLIDE that are considered to be *medically important* are:

Less likely (5 – 20%):
- excess sugar in the blood (hyperglycemia)
- neuromuscular disorders

Rarely (1 – 4%):
- gastrointestinal bleeding (eg in the stomach or intestines)
- hearing loss or ringing in the ears

Lung disorders (including inflammation, pneumonia and fluid collection) have been rarely associated with LEUPROLIDE

Additional risks and side effects associated with GOSERELIN that are considered to be *medically important* are:

Rarely (1 – 4%):
- decreased bone marrow function, may reduce number of infection fighting cells
- flu-like syndrome
- infection

Additional risks and side effects associated with BUSERELIN that are considered to be *medically important* are:

Less likely (5 – 20%):
- depression

Decreased bone density (bone loss) may occur in patients treated with long term LHRH agonists.

Thromboemboli (blood clots) have been rarely associated with the androgen suppression agents used on this trial.

Monitoring (Tests and Questionnaires)

I understand that I must agree to be closely monitored with PSA measurements, bone scans, x-ray work throughout the time that I am on this trial. If I am on the intermittent hormone treatment, failure to do so could allow my cancer to progress more rapidly than it would have if I had remained on continuous hormone treatment. With close and careful monitoring, the chance of this happening is small.

The needles used to take blood or inject substances for body scans might be uncomfortable. You might get a bruise, or rarely, an infection at the site of the needle puncture.

To monitor the effect of hormones on my quality of life, I will be asked to complete a questionnaire (requiring about 30 minutes) at registration for the study, every four months for two years, then every eight months until I develop hormone resistance, at the time of hormone resistance then annually.

<u>The next two paragraphs apply to Canadian patients only</u>

If I am allocated to the intermittent arm, approximately 1 tablespoon of additional blood will be taken with a needle from a vein in my arm before I start the treatment and again if I develop hormone resistance. If I am allocated to the continuous arm, approximately 1 tablespoon of additional blood will be taken at the start of treatment, then annually for 5 years. This blood will be used to measure possible blood indicators that might, in the future, help decide which type of treatment suits which patients better. These samples will be sent to a central review laboratory.

To help study the blood samples I will also be asked to complete a Nutrition Survey prior to treatment.

Possible Benefits

It is not possible to predict if I will personally benefit from participating in this study. The information that is obtained from this study may be used scientifically and may be helpful to others. The possible benefits are improved control of my cancer and prolongation of my life but this is not guaranteed. My quality of life may be improved by the periods off hormonal treatment. If I should suffer side effects or if there is any indication that the treatment is not in my best interest, then it will be stopped and alternative treatments will be discussed.

Risks

There is at present no way of predicting how fast my cancer will grow back during the non-treatment interval. Monitoring is very important to detect regrowth.

Other Treatment Choices

Alternative management which might be considered for prostate cancer like mine would be continuous hormonal treatment, an operation to remove the testicles, or no treatment at all until symptoms occur. My doctor will talk to me about the known benefits and risks of these other treatment options. My doctor can also discuss with me what will happen if I decide not to undertake any treatment at this time.

My participation is entirely voluntary. If I choose to enter this study and at a later date a new and more effective treatment which is suitable for me becomes available, the new treatment will be offered to me. My present and future medical care and treatment or other benefits to which I am entitled will not be affected if I choose not to participate in this study or if I decide to participate and later change my mind and withdraw from this study.

I will be told, in a timely manner, about new information that may affect my health, welfare, or willingness to stay in this study.

How Long Will I Be In The Study?

The researchers can take me off the study treatment early for reasons such as:

- The treatment does not work for me and my cancer gets worse.
- I am unable to tolerate the study treatment.
- New information shows that the study treatment is no longer in my best interest.
- My doctor no longer feels this is the best treatment for me.
- Sponsor decides to stop trial.

Confidentiality, Access to Medical Records

Qualified representatives of the following organizations may inspect and receive information from my medical/study records for quality assurance and data analysis:

- National Cancer Institute of Canada, Clinical Trials Group (NCIC CTG) which is organizing this study.
- Southwest Oncology Group (SWOG) which is organizing US participation in this study.
- Cancer Trials Support Unit (CTSU) at the National Cancer Institute of the US which is organizing US participation in this study.
- Clinical Trials and Statistics Unit of the Institute of Cancer Research (ICR) which is organizing UK participation in this study.
- Food and Drug Administration (FDA) of the US government.
- National Cancer Institute (NCI) of the US which is funding the US cooperative group to coordinate the study.
- Health Canada.
- Multi-Centre Research Ethics Committees (MREC) of the National Health Service (NHS) in United Kingdom.
- Research Ethics Committee.

The organizations listed above will keep the information they see or receive about me confidential, to the extent permitted by applicable laws. Identifying information will never be included in a publication of the research.

Costs

I will not be paid for taking part in this study. Taking part in this study may result in added costs to me.

In the case of research-related side effects or injury, medical care will be provided by my doctor or I will be referred for appropriate medical care.

This section for CTSU participants only.
While I am participating in this study a record of my progress in this study will be kept in a confidential form at [INSERT NAME OF INSTITUTION] and sent to the sponsor who will add this information to a computer file. The confidentiality of any central computer record will be carefully guarded and no information by which I can be identified will be released or published. I have been informed that authorized representatives of the National Cancer Institute of Canada Clinical Trials Group and the Cancer Trials Support Unit (CTSU), the National Cancer Institute, The Food and Drug Administration (FDA), the Therapeutic Products Directorate (TPD of the Health Protection Branch) in Canada and [INSERT NAME OF INSTITUTION AND INSTITUTIONAL REVIEW BOARD HERE] may inspect and copy the records. My identity will remain confidential and my records will be used by these authorized representatives only in connection with carrying out their obligations relating to the clinical trial and they shall not be used for any other purpose or disclosed to any third party except with my express permission.

Further Questions

I have been given a copy of this consent form.

If I have questions about taking part in this study or if I suffer a research-related injury, I can ask my doctor.

Or, I can meet with the doctor who is in charge of the study at this institution. That person is:

_____ _____
Telephone

Or, I can ask questions of the head of the university department. That person is:

_____ _____
Telephone

Or, I can talk to someone who is not involved with the study at all, but who can advise me on my rights as a patient. That person is:

_____ _____
Telephone

My signature on this consent form means that I agree to take part in this study.

_____ _____
Signature of Patient Date

_____ _____
Signature of Investigator Date

Was the patient assisted during the consent process in one of the ways listed below?

☐ Yes ☐ No

<u>If yes</u>, please check the relevant box and complete the signature space below:

☐ The consent form was read to the patient, and the person signing below attests that the study was accurately explained to, and apparently understood by, the patient.

☐ The person signing below acted as a translator for the patient, during the consent process.

_____ _____
Signature of Person Assisting in the Consent Discussion Date

Note: This consent form is available in French on request.

Version date and/or REB approval date of this form: _____	NCIC CTG Pt. Serial #: _____

ÉTUDE RANDOMISÉE DE PHASE III VISANT À COMPARER LE TRAITEMENT ANTIANDROGÈNE INTERMITTENT AVEC LE TRAITEMENT ANTIANDROGÈNE CONTINU CHEZ DES PATIENTS AYANT REÇU UNE RADIOTHÉRAPIE POUR LE CANCER DE LA PROSTATE ET PRÉSENTANT UNE PROGRESSION DE LEUR TAUX D'ANTIGÈNE PROSTATIQUE SPÉCIFIQUE EN L'ABSENCE DE SIGNES CLINIQUES DE MÉTASTASES À DISTANCE

Contexte de l'étude

On m’a demandé de participer à un essai clinique parce que j’ai un cancer de la prostate qui est réapparu après traitement.

Le cancer de la prostate nécessite généralement la présence d'hormones mâles pour se développer. La majeure partie des hormones mâles proviennent des testicules sous forme de testostérone. Cependant, les glandes surrénales produisent aussi une petite quantité d'hormones mâles. Le traitement standard dans des cas comme le mien consiste à supprimer les hormones mâles ou à en bloquer l'action, c'est pourquoi on l'appelle «hormonothérapie». Ce traitement peut consister à enlever les testicules par chirurgie, à bloquer la production de testostérone par des injections tous les 1-4 mois (4-16 semaines) ou par des comprimés à prendre tous les jours, ou une combinaison de ces moyens.

Objectif et description de l'étude

Bien que l'hormonothérapie soit généralement très efficace pour faire régresser (diminuer) le cancer et réduire le taux de PSA (antigène spécifique de la prostate, qui est un marqueur de l'activité du cancer), son effet ne dure pas indéfiniment et le cancer finit par recommencer à progresser malgré une hormonothérapie continue. Cette nouvelle progression du cancer peut se produire quelques mois après le début de l'hormonothérapie ou plusieurs années plus tard. Lorsque cela survient, on parle de résistance à l'hormonothérapie ou «hormonorésistance», et le cancer peut être alors très difficile à maîtriser.

Des études préliminaires ont été effectuées au cours desquelles on a donné une hormonothérapie par cycles, de façon «intermittente», à des hommes ayant un cancer récurrent de la prostate. Ces études ont démontré que les hommes qui ont reçu une hormonothérapie intermittente semblent avoir d'aussi bons résultats que ceux qui ont reçu le traitement standard et peuvent bénéficier d'une meilleure qualité de vie.

On ignore les effets du traitement intermittent sur le développement de la résistance à l'hormonothérapie. Il se pourrait que ce traitement ait un effet néfaste, celui de faire

progresser le cancer en créant un environnement hormonal instable. Cependant, des essais sur les animaux semblent plutôt démontrer que le traitement intermittent pourrait retarder l'apparition de la résistance à l'hormonothérapie en laissant le corps retrouver par périodes un taux normal d'hormones mâles. Selon les études effectuées jusqu'à présent, si ce traitement avait un effet néfaste, il serait relativement faible.

L'objectif de la présente recherche est de comparer l'hormonothérapie continue avec l'hormonothérapie intermittente afin de déterminer si l'hormonothérapie intermittente est aussi efficace et si elle améliore la qualité de vie. Actuellement, personne ne sait quel des traitements serait le meilleur dans mon cas.

Si j'accepte de participer à l'étude, on m'assignera purement au hasard (par un type de répartition appelé «randomisation» un des deux traitements à l'étude, c'est-à-dire l'hormonothérapie continue (traitement standard) ou l'hormonothérapie intermittente.

Je participerai à l'étude jusqu'à ce qu'il soit prouvé que mon cancer a cessé de répondre au traitement (hormonorésistance). Cependant, même après que j'aurai cessé de participer, on continuera de recueillir de l'information sur l'évolution de ma maladie pendant le reste de ma vie.

Environ 1340 patients devraient participer à cette étude.

Description des traitements

Étant donné que plusieurs médicaments semblables seront utilisés dans la présente étude, je comprends que je pourrai discuter avec mon médecin des différents schémas thérapeutiques (doses et fréquence) qui peuvent être utilisés dans mon cas.

Groupe 1 : traitement intermittent

Si on m'assigne par randomisation le traitement intermittent, on me prescrira des comprimés que je devrai prendre tous les jours pendant au moins 4 semaines; en plus, on me fera des injections régulières ou on me mettra des implants sous-cutanés à tous les mois, ou tous les deux mois, ou tous les trois mois, ou tous les quatre mois, selon le médicament employé. À chaque visite, on me prélèvera au plus une cuillerée à soupe de sang pour mesurer mon taux de PSA et pour d'autres analyses de sang. Si mon taux de PSA diminue jusqu'au niveau normal pendant une période de traitement de 8 mois, je pourrai cesser de prendre ces médicaments pendant une période allant de 3 à 12 mois ou plus. La durée exacte de cette période sans traitement dépendra des changements dans mon taux de PSA. Pendant cette période sans traitement, on me surveillera de près et on me fera des analyses de sang tous les 2 mois afin de détecter les premiers signes de changement dans mon taux de PSA. Lorsque mon taux de PSA atteindra un niveau déterminé dans l'étude, je recommencerai à recevoir la même hormonothérapie pendant une autre période de 8 mois. Il est probable que je recevrai plusieurs cycles d'hormonothérapie entrecoupés d'intervalles «sans traitement». Si mon taux de PSA n'est pas

bien régularisé ou encore s'il est démontré que j'ai un nouveau cancer, il se peut que je commence à recevoir un traitement continu semblable à celui que recevront les patients du groupe 2.

Si j'étais sexuellement actif avant de recevoir l'hormonothérapie, il y a 75 % de probabilités que mes fonctions sexuelles recommenceront dans les semaines qui suivront l'interruption de l'hormonothérapie.

Groupe 2 : traitement standard

Si on m'assigne par randomisation le traitement standard, mon hormonothérapie sera continuelle, sans interruption prévue. C'est-à-dire qu'on me fera des injections ou on me mettra des implants sous-cutanés à tous les mois, ou tous les deux mois, ou tous les trois mois, ou tous les quatre mois, selon le médicament employé, ou je subirai une intervention chirurgicale consistant à m'enlever les testicules et je devrai, dans certains cas, prendre des comprimés chaque jour. Je devrai prendre ces comprimés pendant au moins 4 semaines. À chaque visite, on me prélèvera au plus une cuillerée à soupe de sang pour mesurer mon taux de PSA et pour d'autres analyses de sang.

Risques et effets secondaires possibles

Effets secondaires

Pendant que vous participerez à l'étude, vous risquez d'éprouver les effets secondaires énumérés ci-dessous. Il faut en discuter avec votre médecin. Comme dans le cas de tout traitement expérimental combiné, d'autres effets secondaires inattendus et parfois graves peuvent faire leur apparition.

Comme on ne connaît pas les effets que le traitement peut avoir sur un fœtus, il ne faut pas procréer pendant que vous participez à cette étude. Il faut utiliser une méthode contraceptive efficace pendant que vous recevez le traitement à l'étude.

Votre médecin vous suivra de près pour déceler tout effet secondaire. Lorsque ce sera possible, on vous administrera d'autres médicaments pour atténuer les effets secondaires et les rendre moins inconfortables. Beaucoup d'effets secondaires disparaissent peu après l'arrêt du traitement, mais ils peuvent dans certains cas être sérieux, durer longtemps ou être permanents.

Les médicaments que vous pourrez recevoir seront des agents hormonaux, soit un anti-androgène et un agoniste de la gonadolibérine. Ces médicaments agissent sur le cancer de la prostate en nuisant à l'action des hormones masculines sur les cellules cancéreuses de la prostate. Il y a plusieurs agents hormonaux anti-androgènes et agonistes de la gonadolibérine disponibles pour traiter le cancer de la prostate et votre médecin vous dira lequel vous recevrez. En général, ces médicaments causent des effets secondaires reliés à la suppression des effets des hormones masculines. Votre médecin vous informera des effets secondaires particuliers des agents hormonaux que l'on vous prescrira.

Risques et effets secondaires des agents ANTI-ANDROGÈNES (Bicalutamide, Flutamide, Nilutramide, Cyproterone (Androcur)) à l'étude :

Très probables (21 % ou plus) :
- bouffées de chaleur;
- impotence, baisse de la libido;
- nausées, vomissements.

Moins probables (5 à 20 %) :
- développement excessif des seins chez les hommes qui peut inclure la sensibilité des seins;
- changements de la tension artérielle (hypertension ou hypotension);
- enflure causée par l'accumulation excessive de liquide dans les tissus;
- étourdissements;
- difficulté à dormir;
- éruptions et démangeaisons;
- constipation;
- diarrhée;
- diminution du nombre des globules rouges qui transportent l'oxygène;
- résultats élevés aux tests de fonction hépatique qui peuvent causer la jaunisse.

Rares (1 à 4 %) :
- maux de tête;
- somnolence;
- changements de l'appétit;
- changements des résultats d'analyses sanguines associés à la fonction rénale;
- diminution de la fonction de la moelle osseuse qui peut réduire le nombre des globules luttant contre les infections;
- cardiopathie, y compris insuffisance cardiaque et crise cardiaque.

Risques et effets secondaires supplémentaires associés au BICALUTAMIDE jugés *médicalement importants* :

Moins probables (5 à 20 %) :
- engourdissement et picotements aux mains et aux pieds;
- concentration excessive de sucre dans le sang (hyperglycémie);
- symptômes ressemblant à ceux de la grippe;
- infection;
- difficulté à respirer;
- présence de sang dans l'urine.

Rares (1 à 4 %) :
- inflammation aiguë des poumons (maladie pulmonaire interstitielle).

Risques et effets secondaires supplémentaires associés au FLUTAMIDE jugés *médicalement importants* :

Rares (1 à 4 %) :
- confusion;
- vision floue;
- inflammation du foie qui peut nuire à la fonction hépatique;
- l'exposition à la lumière peut causer l'apparition de rougeurs, de cloques et d'ulcères de la peau (photosensibilité).

On a rarement associé le *cancer du sein* au flutamide.

IL FAUT ÉVITER LE PAMPLEMOUSSE ET LE JUS DE PAMPLEMOUSSE pendant toute la durée du traitement au FLUTAMIDE, car ils peuvent réagir avec cet agent.

Risques et effets secondaires supplémentaires associés au NILUTAMIDE jugés *médicalement importants* :

Moins probables (5 à 20 %) :
- photophobie (incapacité de s'adapter à un changement subit d'éclairage).

Rares (1 à 4 %) :
- problèmes respiratoires (souffle court, toux);
- inflammation aiguë des poumons (maladie pulmonaire interstitielle);
- pneumonite (peut inclure la toux, l'essoufflement, des douleurs à la poitrine ou de la fièvre);
- douleurs abdominales ou abdomen sensible;
- symptômes ressemblant à ceux de la grippe;
- concentration excessive de sucre dans le sang (hyperglycémie);
- intolérance à l'alcool.

Risques et effets secondaires supplémentaires associés au CYPROTERONE jugés *médicalement importants* :

- fatigue;
- faiblesse;
- problèmes respiratoires (essoufflement à l'effort, toux);
- vision floue, photophobie;
- dépression;
- chute des cheveux et des poils;
- concentration excessive de sucre dans le sang (hyperglycémie);
- insuffisance hépatique;
- formation de tissu cicatriciel dans les poumons (fibrose pulmonaire);
- ostéoporose.

Risques et effets secondaires communs à deux ou plus des agonistes de la gonadolibérine (leuprolide, goséréline, busséréline) utilisés au cours de l'étude :

Très probables (21 % ou plus) :

- bouffées de chaleur;
- impotence, baisse de la libido;
- nausées, vomissements;
- douleur.

Moins probables (5 à 20 %) :

- fatigue;
- envie accrue d'uriner et besoin d'uriner plus souvent;
- diminution de la grosseur des testicules;
- développement excessif des seins chez les hommes qui peut inclure la sensibilité des seins;
- changements de la tension artérielle (hypotension ou hypertension) qu'on a rarement associés à des accidents vasculaires cérébraux;
- étourdissements, qui peuvent inclure le vertige (pièce qui tourne);
- difficulté à dormir;
- engourdissement et picotements aux mains et aux pieds;
- rougeur de la peau et irritation au point d'injection;
- constipation;
- difficulté à respirer;
- diminution ou perte de force;
- maux de tête;
- douleurs musculaires;
- douleurs articulaires;
- douleurs osseuses;
- changements des concentrations de lipides et de protéines dans le sérum;
- battements cardiaques irréguliers;
- changements de l'appétit.

Rares (1 à 4 %) :

- enflure causée par l'accumulation excessive de liquide dans les tissus;
- éruption qui démange;
- diarrhée;
- prise ou perte de poids;
- élévation des résultats des tests de fonction hépatique;
- toux;
- réaction de flambée de maladie (douleurs osseuses accrues, blocage des voies urinaires et compression de la moelle épinière qui peut causer de la douleur, des picotements dans les bras et les jambes et des problèmes de locomotion et de sensation, qui incluent rarement la paralysie);
- cardiopathie, y compris insuffisance cardiaque et crise cardiaque;
- tumeur bénigne à l'hypophyse (adénome pituitaire);
- fièvre;
- changements de la vision;

- perte de mémoire;
- réaction allergique qui peut inclure, dans des cas graves, le choc anaphylactique (caractérisé par une tension artérielle très basse, une mauvaise alimentation en sang des tissus et la difficulté à respirer).

Risques et effets secondaires supplémentaires associés au LEUPROLIDE jugés *médicament importants* :

Moins probables (5 à 20 %) :
- concentration excessive de sucre dans le sang (hyperglycémie);
- troubles neuromusculaires.

Rares (1 à 4 %) :
- saignement gastro-intestinal (p. ex., dans l'estomac ou les intestins);
- perte d'audition ou tintements dans les oreilles.

On a rarement associé des *troubles pulmonaires* (y compris inflammation, pneumonie et accumulation de liquide) au LEUPROLIDE.

Risques et effets secondaires supplémentaires associés à la GOSÉRÉLINE jugés *médicalement importants :*

Rares (1 à 4 %) :
- réduction de la fonction de la moelle osseuse qui peut réduire le nombre de cellules luttant contre les infections;
- symptômes ressemblant à ceux de la grippe;
- infection.

Risques et effets secondaires supplémentaires associés à la BUSÉRÉLINE jugés *médicalement importants* :

Moins probables (5 à 20 %) :
- dépression.

Une diminution de la densité osseuse (fonte osseuse) est possible chez les patients qui suivent un traitement de longue durée aux agonistes de la gonadolibérine.

On a rarement associé des *thrombo-embolies* (caillots de sang) aux agents anti-androgènes utilisés au cours de cette étude.

Surveillance (examens et questionnaires)

Je comprends que je dois accepter d'être surveillé de près; en effet, on mesurera mon taux de PSA et on me fera passer des scintigraphies osseuses (scans) et des radiographies aussi longtemps que je participerai à l'étude. Si je fais partie des patients qui reçoivent l'hormonothérapie intermittente et si je ne suis pas surveillé de près, cela pourrait permettre à mon cancer de progresser plus rapidement que si je recevais l'hormonothérapie continuelle. Cependant, le risque que cela se produise est faible si je suis surveillé de près.

Les aiguilles utilisées pour prélever du sang ou injecter des substances pour les examens radiologiques peuvent provoquer de l'inconfort. Elles peuvent causer une ecchymose (un bleu) ou, rarement, une infection à l'endroit de la piqûre.

Afin de vérifier l'effet des hormones sur ma qualité de vie, on me demandera de répondre à un questionnaire (d'environ 30 minutes) au moment de mon inscription à l'étude, tous les quatre mois pendant deux ans, puis tous les huit mois aussi longtemps que je n'aurai pas développé de résistance à l'hormonothérapie, au moment où on constatera une résistance à l'hormonothérapie, puis une fois par année.

<u>Les deux paragraphes suivants concernent seulement les patients canadiens.</u>

Si je fais partie du groupe de patients qui reçoivent le traitement intermittent, on me prélèvera en plus environ une cuillerée à soupe de sang par ponction veineuse pratiquée dans un bras avant le début du traitement et au moment où on constatera, le cas échéant, que j'ai développé une résistance à l'hormonothérapie. Si je fais partie du groupe de patients qui reçoivent le traitement continu, on me prélèvera en plus environ une cuillerée à soupe de sang au début du traitement, puis une fois par année pendant 5 ans. Le sang prélevé servira à mesurer des indicateurs sanguins qui pourraient, à l'avenir, aider à déterminer quel traitement convient le mieux à un patient donné. Ces échantillons seront envoyés à un laboratoire central pour y être examinés.

Afin de pouvoir mieux analyser mes échantillons de sang, on me demandera aussi de remplir, avant le traitement, un questionnaire sur mon alimentation.

Avantages possibles

Personne ne peut prédire si je retirerai un avantage quelconque de ma participation à cette étude. L'information obtenue grâce à cette étude pourrait servir au niveau scientifique et être utile à d'autres patients. Les avantages possibles sont une meilleure maîtrise de mon cancer et une espérance de vie plus longue, mais cela n'est pas certain. Il est possible que ma qualité de vie soit meilleure pendant les périodes d'interruption de l'hormonothérapie. Si j'ai des effets secondaires et s'il y a des indications que le traitement que je reçois n'est pas dans mon meilleur intérêt, le traitement sera interrompu et on discutera des autres possibilités de traitement.

Risques

Il n'existe aucun moyen de prédire pendant combien de temps mon cancer demeurera inactif pendant la période sans traitement suivant un cycle d'hormonothérapie. C'est pourquoi la surveillance est essentielle pour détecter toute progression du cancer.

Autres choix de traitement

Les autres choix de traitement pour les patients ayant un cancer de la prostate comme le mien sont l'hormonothérapie continuelle, l'ablation (enlèvement) des testicules ou l'absence de traitement jusqu'à l'apparition des symptômes. Mon médecin me parlera des avantages et des risques connus de ces autres traitements possibles. Il peut aussi discuter avec moi de ce qui se passera si je décide de ne pas entreprendre de traitement pour le moment.

Ma participation à l'étude est tout à fait volontaire. Si je choisis de participer à l'étude et si un nouveau traitement plus efficace devient disponible plus tard au cours de l'étude, on m'offrira le nouveau traitement. Si je choisis de ne pas prendre part à l'étude ou si j'accepte de participer mais que je change d'idée plus tard et je décide de me retirer, cela n'aura aucune influence sur les soins et les traitements médicaux que je reçois ou que je recevrai, ni sur les autres privilèges auxquels j'ai droit.

On me communiquera, en temps et lieu, les nouveaux renseignements qui peuvent avoir un effet sur ma santé, mon mieux-être ou ma volonté de continuer de participer à l'étude.

Pendant combien de temps participerai-je à l'étude?

Les chercheurs peuvent mettre fin plus tôt que prévu au traitement qui fait partie de l'étude, pour des raisons comme les suivantes :

- Le traitement ne donne pas de résultat dans mon cas et mon cancer s'aggrave.
- Je suis incapable de tolérer le traitement à l'étude.
- De nouveaux renseignements disponibles montrent que le traitement à l'étude n'est plus dans mon meilleur intérêt.
- Mon médecin ne croit plus que le traitement à l'étude soit le meilleur pour moi..
- Le commanditaire décide de mettre fin à l'étude.

Confidentialité et accès aux dossiers médicaux

Des représentants qualifiés des organisations suivantes peuvent inspecter mes dossiers médicaux ou ceux de l'étude et en recevoir de l'information pour des fins d'assurance de la qualité et d'analyse des données :

- le Groupe des essais cliniques de l'Institut national du cancer du Canada (GEC-INCC) qui organise la présente étude;
- le Southwest Oncology Group (SWOG) qui organise le volet américain de l'étude;
- l'Unité de soutien aux études sur le cancer (CTSU) de l'Institut national du cancer des États-Unis, qui organise la participation des États-Unis à cette étude.;
- l'Unité des études cliniques et de la statistique de l'Institut de recherche sur le cancer (ICR), qui organise la participation du R.-U. à cette étude;
- la Food and Drug Administration du gouvernement américain;
- le National Cancer Institute des États-Unis qui finance le groupe coopératif américain qui coordonne l'étude;
- Santé Canada;
- les comités multicentriques d'éthique en recherche (MREC) du Service national de la santé (NHS) du Royaume-Uni;
- le comité d'éthique pour la recherche.

Les organisations mentionnées ci-dessus maintiendront la confidentialité des renseignements qu'elles voient ou reçoivent à mon sujet, dans la mesure où les lois pertinentes le permettent. Aucune publication sur la recherche ne contiendra de renseignements permettant de vous identifier.

Coûts

Je ne toucherai aucun paiement pour participer à l'étude. La participation à cette étude pourrait m'imposer des frais supplémentaires.

En cas d'effets secondaires ou de traumatisme relié à la recherche, mon médecin me dispensera des soins médicaux, ou l'on m'aiguillera vers les soins médicaux nécessaires.

La section suivante s'adresse seulement aux patients qui participent à l'étude dans les établissements associés au CTSU.

Pendant que je participerai à cette étude, on conservera un dossier confidentiel sur l'évolution de ma maladie à [INSÉRER LE NOM DE L'ÉTABLISSEMENT] et ce dossier sera envoyé au commanditaire qui entrera cette information dans un ordinateur. On prendra grand soin de conserver la confidentialité de tous les dossiers contenus dans cet ordinateur central et aucune information permettant de m'identifier ne sera divulguée ni publiée. On m'a informé qu'il est possible que des représentant(e)s autorisé(e)s du Groupe des essais cliniques de l'Institut national du cancer du Canada, l'Unité de soutien aux études sur le cancer (CTSU) de l'Institut national du cancer des États-Unis, de la Food and Drug Administration (FDA) des États-Unis, de la Direction des produits thérapeutiques (DPT de la Direction générale de la protection de la santé) du Canada et de [INSÉRER LE NOM DE L'ÉTABLISSEMENT ET DU COMITÉ D'ÉTHIQUE LOCAL] révisent et copient ces dossiers. Mon identité demeurera confidentielle et ces représentant(e)s autorisé(e)s utiliseront mes dossiers seulement pour s'acquitter de leurs obligations relatives à l'essai clinique. Ils (elles) ne pourront pas utiliser mes dossiers dans d'autres buts ni les divulguer à d'autres personnes sans mon autorisation expresse.

Date de la version de ce formulaire ou date d'approbation par le CER : _____	N^{o} série Pt GEC INCC : _____

Autres questions

On m'a remis un exemplaire du présent formulaire de consentement.

Si j'ai des questions concernant ma participation à l'étude ou si je subis un traumatisme relié à la recherche, je peux les poser à mon médecin.

Je peux aussi poser mes questions au responsable de l'étude dans l'établissement où je suis suivi. Il s'agit de :

_____ _____
Nom Téléphone

Je peux aussi poser mes questions au chef du département universitaire responsable. Il s'agit de:

_____ _____
Nom Téléphone

Ou encore, je peux parler de ma participation à l'étude à une personne qui n'est aucunement reliée à l'étude et qui peut me conseiller sur mes droits en tant que patient. Il s'agit de :

_____ _____
Nom Téléphone

Ma signature au bas du présent formulaire indique que j'accepte de participer à l'étude.

_____ _____
Signature du patient Date

_____ _____
Signature duchercheur Date

_____ _____

A-t-on aidé le patient d'une des façons indiquées ci-dessous pendant le processus visant à obtenir le consentement?

☐ Oui ☐ Non

Si oui, veuillez cocher la case pertinente et remplir l'espace réservé à la signature ci-dessous :

☐ On a lu le formulaire de consentement au patient et la personne qui appose sa signature ci-dessous atteste qu'on a expliqué précisément l'étude au patient, qui semble l'avoir comprise.

☐ La personne qui appose sa signature ci-dessous a fait fonction d'interprète pour le patient au cours du processus visant a obtenir le consentement.

_____ _____
Signature de la personne qui a participé à la discussion sur le consentement Date

Note : Ce formulaire de consentement est disponible en anglais.

Date de la version de ce formulaire ou date d'approbation par le CER : _____	N^{o} série Pt GEC INCC : _____

APPENDIX XIII- NCIC CTG LIST OF "CONTACTS"

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to the telephone call to request an allocation.	Barbara Mayer Clinical Trials Assistant NCIC CTG Email: bmayer@ctg.queensu.ca	613-533-6430	613-533-2941
DATA MANAGEMENT INQUIRES (including CRF completion questions and query letters)	Al Le, Karen Somers, Lisa Kenney Research Associates NCIC CTG Email: ale@ctg.queensu.ca ksomers@ctg.queensu.ca lkenney@ctg.queensu.ca		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	PR.7 Study Coordinator NCIC CTG Email:		
	or: Dr. Chris O'Callaghan Project Coordinator NCIC CTG Email: cocallaghan@ctg.queensu.ca		
STUDY CHAIRS	Dr. Juanita Crook Study Chair Email: juanita.crook@rmp.uhn.on.ca	416-946-2125	416-946-6556
	or: Dr. Laurence Klotz Study Chair Email: laurence.klotz@swchsc.on.ca	416-480-4673	416-480-6002
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	PROTOCOL Study Coordinator NCIC CTG	613-533-6430	613-533-2941