1.0 Objectives

a. To determine if one year of adjuvant hormonal ablation in node negative radical prostatectomy patients at high risk for progression will result in an improvement in disease-free survival at five years.

b. To determine the impact of one year of total androgen ablation on quality of life.

c. To assess differences in quality of life between wives/partners of patients in the androgen ablation condition compared to wives/partners of patients in the control condition.

d. To obtain blood samples and tissue blocks from tumor and normal prostate from patients at high risk for post prostatectomy to evaluate markers of prognosis.

2.0 Background

Radical prostatectomy has become the treatment of choice for many patients with organ confined prostate cancer (AJCC T1-T2) who have at least a ten year life expectancy. Data from surgical series suggest that 10-15 year overall survivorship of 88-64% (respectively) can be achieved with disease-free survivorship ranging from 72-62% in patients with negative lymph nodes (1-3). Serum prostate specific antigen (PSA) testing has redefined the threshold for surgical cure of prostate cancer. Since PSA is produced exclusively by prostate tissue (benign and malignant) surgical removal of the gland should result in an undetectable value. Failure of the serum PSA to become undetectable post radical prostatectomy or a subsequent rise from a prior undetectable value is now considered to represent treatment failure (4). PSA recurrence (biochemical failure) has been shown to invariably antedate clinically recognized disease by several months, or even years depending on site of relapse and the biological aggressiveness of the disease. Thus, serum PSA represents the earliest known marker for disease recurrence and heralds clinical relapse (4, 5).

Overall, freedom from any relapse (PSA or clinical) in patients treated with radical prostatectomy ranges from 61-87% and 41-71% (respectively) at 5-10 years in mature surgical series (6, 7). Surgical cure of patients with clinically organ-confined (T1-T2) cancer (as evidenced by an undetectable PSA at 5 years) is related to the grade (Gleason score), PSA, pathologic stage (pT1-2, versus pT3 or positive lymph nodes) and surgical margin status of the cancer (6-10). Patients with well differentiated (Gleason score 2-6), organ-confined cancers with a serum PSA of less than 10 ng/ml, can expect an 83-95% freedom from any relapse over a five-year period (7). Alternatively, patients with a preoperative PSA >20 ng/ml, Gleason score >8, seminal vesicle involvement, extensive positive surgical margins, or lymph node involvement have at least a 50 percent chance of biochemical relapse within 5 years (7-10). Of interest, many of these criteria also identify subsets of patients at risk for failure of definitive external beam radiation

therapy (11). Thus, patients at "high" risk for failure with standard local therapies can be stratified by the above clinicopathologic variables.

Of these variables, the presence of pelvic lymph node involvement at the time of radical prostatectomy is the most adverse and is virtually synonymous with systemic disease as 85% of surgically treated patients have either a rising PSA or distant metastasis by 5 years (12). As such, systemic therapy with hormonal ablation is routinely initiated (with or without local therapy) and has been shown to result in a substantial increase in the interval to progression (13). The results of recent nonrandomized retrospective studies suggest that the further addition of local control (with radical prostatectomy or external beam radiotherapy) together with early hormonal ablation may represent a therapeutic advance in patients with limited regional metastases (14, 15). Messing et al have shown that adjuvant long term hormonal therapy instituted immediately after RP (in those patients with microscopic lymph node metastases) is associated with improved survival when compared to surgery alone with delayed hormonal therapy (16)

The optimal management of surgically treated patients with negative lymph nodes (at surgery), but who remain at high risk for clinical or biochemical failure (Gleason score >8, seminal vesicle involvement, extensive positive surgical margins) remains problematic. Data from two recent series from Johns Hopkins and the Mayo Clinic revealed that in this cohort of men, the 5-year disease free survival ranged from 44-49% (17-18). A more recent series from M.D. Anderson Cancer Center noted a higher 5-year disease free survival (68%), which may be related to the higher incidence of organ and specimen confined high grade cancers. (19) In a recent series of 2404 men that underwent radical prostatectomy, it was noted that the sites of relapse were distant (33%), local (9%), and rising PSA only in 58% of men (17). Adjuvant radiation therapy in this setting would only potentially benefit a subset and would not address systemic "micrometastases" which may contribute to biochemical failure. In fact, two studies suggest that of patients undergoing adjuvant radiation therapy post-prostatectomy in the setting of positive seminal vesicles or high grade disease only 37-45% are free from relapse at five years, suggesting little beneficial effect (20-21). The primary objective of the current protocol is to determine if one year of adjuvant hormonal ablation (which possesses local and systemic antitumor effects) in node negative radical prostatectomy patients at high risk for progression will result in an improvement in disease-free survival at five years.

Hormonal ablation will be accomplished by administration of the luteinizing hormone releasing hormone agonist (LH-RH) Goserelin (Zoladex®) in combination with the nonsteroidal antiandrogen Bicalutamide (Casodex®) to produce total androgen blockade. Total androgen blockade is routinely utilized in the clinical management of prostate cancer patients. The rationale is based on lowering serum testosterone levels into the castrate range utilizing either orchiectomy or an LH-RH agonist. An antiandrogen is added to negate the effects of adrenal androgens by competitively binding to the androgen receptor. In three large early clinical trials total androgen ablation was shown to prolong progression free and over all survival by 3-12 months and 7 months respectively (22-24). However, patients with minimal metastatic disease were noted to receive the most benefit. Recently, the magnitude of the clinical benefit of total androgen

blockade has been questioned. A collaborative mega-analysis of 27 randomized trials involving 8,275 men (98% of those were randomized in trials of total androgen blockade versus monotherapy) revealed an overall 5 year survival benefit of only 2-3% (25). Among such trials, the randomized study of orchiectomy and flutamide versus orchiectomy alone (NCI-INT-0105) revealed no survival benefit for the antiandrogen cohort when patients underwent surgical castration.(26). These results were significantly different than those obtained when the mode of androgen suppression used in prior randomized trial was an LH-RH agonist (22). Thus current opinion favors the fact that an antiandrogen blocks the testosterone "flare" phenomenon and probably makes the LH-RH agonist a safer drug. However, when orchiectomy is used for testosterone suppression an antiandrogen is probably unnecessary.

Total androgen blockade has been evaluated in conjunction with radical prostatectomy in the neoadjuvant setting. For such patients, reversible androgen suppression (i.e., nonsurgical castration) is the optimal approach. Several randomized studies initially reported a decrease in the incidence of positive surgical margins with three months of neoadjuvant hormonal therapy in "clinically" confined prostate cancer. (27-29). However, with long term follow-up there has been no improvement in disease free survival using the three month neoadjuvant hormonal therapy approach. (30) With regards to the timing of androgen ablation, a recent study by Gleave et al. suggested that 8 months of neo-adjuvant androgen ablation (compared with 3 months) resulted in an optimal PSA nadir prior to surgery (31) A follow-up randomized prospective evaluation of three versus 8 months of androgen ablation prior to RP has shown an initial benefit with respect to PSA nadir, prostate volume and positive surgical margins in favor of 8 months of therapy (32). If the enhanced nadir PSA values and negative surgical margins were reflective of enhanced tumor destruction, then perhaps longer periods of androgen ablation may be advantageous. <u>This type of data provides a rationale to prospectively define the effect of one year of adjuvant hormonal therapy post radical prostatectomy</u>. It is hypothesized that a proportion of "high risk" patients will exhibit residual prostate cancer cells that are predominantly androgen sensitive and that one year of therapy will be adequate therapy to induce cell death in this population.

<u>Total androgen ablation as an adjuvant treatment in lymph node negative radical prostatectomy patients has not been studied in a prospective randomized fashion.</u> In addition, the optimal duration of therapy is also unknown. Several prospective randomized studies in patients receiving adjuvant androgen ablation subsequent to external beam radiation therapy have found that the incidence of local, distant, and biochemical failure was significantly decreased when compared with patients receiving delayed hormonal ablation at relapse subsequent to radiation therapy (33). Further, survival in patients with high Gleason grade cancers was enhanced at five years (33-35). Whether the same data would be obtained in a radical prostatectomy population is unknown and needs to be assessed. Preliminary data from the Casodex Early Prostate Cancer program are encouraging in this regard (36). A total of 3603 men received 150mg Casodex (high dose anti androgen) or placebo orally as an adjuvant after RP or radiotherapy or as primary therapy versus placebo in those not receiving definitive therapy. At a median follow-up of

2.6 years, adjuvant monotherapy with Casodex reduced the incidence of objective progression by 43% (16 versus 10%, p <0.0001 [36]).

Thus the proposed study will expand our knowledge base, with respect to the efficacy of a defined period of total androgen blockade in patients at risk for failure due to microscopic local or distant disease post RP. The study is timely in that there is no consensus on the optimal therapy (or its duration) in patients with adverse pathology post radical prostatectomy.

The third and fourth study objectives will be to conduct a companion quality of life study. We will assess the quality of life in patients during and following such treatment utilizing the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (37), the Profile of Mood States (POMS) (38), the UCLA Sexual Functioning Scale (39), the Dyadic Adjustment Scale (40), and the Southwest Oncology Group (SWOG) Treatment Specific Symptom Checklist, developed for the flutamide trial. We also will assess patient preferences (utilities) for treatment outcomes related to androgen ablation, and conduct a quality of life study among the wives/partners of trial participants.

2.1 Androgen ablation in prostate cancer patients and quality of life

The quality of life component of this study is critical. Patient quality of life is increasingly considered an important outcome measure in clinical cancer control studies (41). To date, the effect of androgen ablation on the quality of life of relatively healthy men (i.e., men who do not have metastatic disease) is not well studied. The side effects of androgen ablation therapy may have considerable quality of life implications -- impotence and loss of libido, for example, hot flashes, breast enlargement and tenderness, and feminine distribution of fat deposits (42-44). Herr et al. (45) studied men with asymptomatic, metastatic prostate cancer who chose either androgen ablation or watchful waiting. At six months, they found that those who chose androgen ablation had more sexual dysfunction (problems with erection and interest and enjoyment of sex), physical symptoms (including urinary problems, hot flashes, appetite, nausea and vomiting, sleep, and breast enlargement), and fatigue than men who chose no therapy. The groups did not differ in other dimensions of quality of life. Kornblith et al. (46) surveyed a convenience sample of men with prostate cancer: 14 (late and early-stage disease) had received no treatment, 35 (earlier stage disease) had had prostatectomy or radiation only, and 61 (later stage disease) had received hormonal therapy. A multivariate analysis of variance found an overall significant difference across all dependent measures, with the hormonal therapy groups reporting the worst quality of life. According to the univariate analysis, the groups differed significantly on physical functioning, physical symptoms, and sexual problems. Differences in fatigue, psychological distress, and impact on family/social life were not significant in the univariate analysis, but scores were worse in the hormonal therapy group. Studies of different forms of androgen ablation generally show that patients experience decreases in sexual functioning and marital satisfaction with some improvement in symptoms and overall quality of life (47,48).

The current literature on quality of life and androgen ablation is limited by the use of non-randomized designs, nonstandardized measures (especially to measure marital and sexual functioning), small sample sizes, and an exclusive focus on men with advanced disease. This randomized trial provides us with a unique opportunity to document the effects of early androgen ablation on quality of life. We will use well-validated quality of life measures to assess the life functions that we expect to be most affected by the hormonal therapy: sexual functioning, fatigue, emotional well-being, physical functioning, and treatment-specific symptoms. However, because so little is known about the effect of hormonal therapy on the quality of life of men with local disease, we will monitor other dimensions of quality of life to learn whether they are affected by the treatment as well.

2.3 Quality of life of patients' wives/partners

We will also study the quality of life of the patients' wives and partners* because wives are likely to be the primary caregivers of men with prostate cancer. The stress of caregiving may significantly affect their quality of life and emotional well being; this is also true for the side effects associated with androgen ablation (e.g., decreased sexual functioning).

Caregiving constitutes a chronic stressor independent of the diagnostic category of the patient (54-56); the evidence is strong that caregiving can have many negative effects on the caregiver, including the development of sleep disturbances, anxiety, depression, and a sense of helplessness (54,55,57). The current shift away from inpatient treatment and toward shorter hospitalization has placed even greater responsibility on family caregivers. There is evidence, moreover, that some cancer patients' spouses may be more emotionally distressed than the patients and remain so for even longer than the patients (46, 58-60). Frequently, the spouse's distress level is related to the seriousness of the patient's condition (61-65).

When a patient experiences side effects from androgen ablation therapy, it can influence the quality of life of his wife as well. The patient's lack of sexual desire and impotence will affect the sexual life of the wife, and the couple's sexual problems may lead to or aggravate marital discord. The literature suggests that assessing sexual functioning of cancer patients only, and not their partners, provides an incomplete picture (42). Fatigue resulting from a patient's treatment may increase the burden on the wife for caregiving and household tasks, and it may affect the couple's social contact. Kornblith et al. (46) found that the patients' symptoms, particularly fatigue and urinary frequency, were significantly correlated with the wives' quality of life.

* We will use the term wives to refer to this group, although female partners who have had an intimate relationship with the patient for more than 2 years will be included as well.

Previous approaches to evaluating spousal influence on the patient's quality of life have not reflected the dyadic nature of the behavioral process (46,53,66). The focus has been on the patient or on the spouse, rather than on both simultaneously. Dyadic interaction models (67-69) account for the dynamic nature of the couple's relationship, in which, for example, one member's quality of life influences the quality of life of the other. The direction of the influence, termed *dominance*, provides information about the interplay between spouses in the marital relationship. *Direct dominance* is exhibited in a relationship if the behavior or feelings of one member of the couple predicts the future behavior or feelings of the other. We expect that a patient's symptomatology will directly influence the psychological well being of his wife. *Indirect dominance* refers to the situation in which the behavior or feelings of one member of the couple predicts the couple's future interactions. The study will examine the couple as an interacting unit with varying degrees and directions of influence. Direct dominance and indirect dominance will be evaluated for each aspect of quality of life that is measured. The possibility that different levels of dominance occur as a result of the treatment the patient is receiving will be investigated.

3.0 Background Drug Information and Adverse Events

Goserelin Acetate (Zoladex) contains a potent synthetic decapeptide analogue of luteinizing hormone releasing hormone (LHRH) analogue. Zoladex 10.8mg implant is supplied as a sterile biodegradeable product containing Goserelin acetate equivalent to 10.8mg of Goserelin. It is designed for subcutaneous administration with a continuous release over a 12-week period. (70)

Following administration, Zoladex causes an initial increase in serum luteinizing hormone and follicle stimulating hormone levels. With subsequent increases in serum testosterone. Chronic administration of Zoladex leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in castrated men.

Leuprolide is a synthetic nonapeptide analogue of LH-RH that inhibits pituitary gonadotropin secretion. Leuprolide administration causes an initial increase in gonadotropin secretion and serum testosterone levels, however, serum testosterone levels fall over a 2-4 week period into the range seen in surgically castrated patients. Both long term endocrine and objective tumor responses are similar in advanced prostate cancer patients treated with either orchiectomy or Leuprolide (70).

Bicalutamide is an orally active nonsteriodal antiandrogen with negligible gastrointestinal intolerance and the convenience of once-daily dosing (71-72).

The most frequent adverse event noted for patients with metastatic prostate cancer treated with the combination of a LH-RH analogue and an antiandrogen has been hot flashes (49%). Other adverse events occurring in ≥10% of these patients included abnormal liver function tests, nocturia, diarrhea, nausea, pain and constipation (71). In a recently reported multicenter trial, diarrhea was the most frequently reported adverse experience leading to treatment withdrawal and occurred in 6% of patients receiving flutamide in combination with an LH-RH agonist (72). This same side effect occurred in only 0.5% of patients when bicalutamide was used as the antiandrogen (72). Life threatening flutamide-

associated hepatotoxicity has been reported at a rate of approximately 3/10,000 patients (70,73). It is recommended that liver function tests be monitored and if elevated to 2x normal value in the absence of other reasons that the antiandrogen be discontinued. Hepatotoxicity is usually reversible in this setting. Occasionally prolongation of prothrombin times have been noted in patients receiving warfarin therapy after flutamide is initiated. Thus, in this setting prothrombin times should be routinely monitored. Similar precautions are also advised when bicalutamide is administered. (See Appendix D for additional pharmaceutical details on Goserelin and bicalutamide).

Based upon the final analysis of the double blind trial that compared an LH-RH (Goserelin or Leuprolide) together with either bicalutamide or flutamide, there was no significant difference in either time to progression or survival for either regimen, however, the bicalutamide group had less treatment withdrawal due to diarrhea (72).

4.0 Patient Eligibility

4.1 Clinical Trial

4.1.1 Organ confined prostate cancer subsequent to clinical staging (T1-T2C).

4.1.2 Radical prostatectomy, bilateral pelvic lymph node dissection performed.

4.1.3. Patients may have received up to 3 months of reversible androgen ablation prior to radical prostatectomy (i. e, no surgical castration).

4.1.4 Pathologic assessment of surgical specimens by M. D. Anderson Cancer Center pathologist.

4.1.4a The M. D. Anderson pathologist will review the prostatectomy specimen including the pelvic lymph nodes. For patients who received androgen ablation prior to the prostatectomy the pre-treatment biopsy will also be evaluated to determine the Gleason score.

All stained sections from the radical prostatectomy specimen including pelvic lymph nodes and the appropriate institutional pathology reports should be submitted. The material submitted should also include any special stains performed. If the patient received pre – op hormonal ablation therapy, all the slides from the pretreatment biopsy should also be submitted to the review center. In addition, a representative block of the tumor and a block of normal prostate from the prostatectomy specimen should be included. For patients treated pre-operatively with hormonal ablation a block of tumor and a block of normal tissue from the pre-treatment biopsy should also be submitted. The slides will be returned to the submitting institution. The blocks will be retained at M. D. Anderson for the future evaluation of markers of progression.

If the blocks received are not considered representative of the tumor, different block/s will be requested of the contributing pathologist and the originally received block/s will be returned upon receipt of the new block/s.

Note: The blocks of tumor should be representative of the tumor with the highest histologic grade.

4.1.4b Slides, blocks and pathology report/s should be sent to the MDACC within 48 hours of registration via overnight express to:

MD Anderson Cancer Center
Data Management Center
1100 Holcombe Blvd-**Rm 3.100**
Houston, TX 77030

4.1.4c Pathologic data will be recorded on the attached report form. A copy of the completed report form will be sent to the contributing pathologist.

4.1.4d Pathologic criteria for eligibility include:

For patients <u>with</u> (up to 3 months) prior androgen ablation:

a) Gleason score ≥ 8 on pretreatment biopsy, (or)
b) Seminal vesicle invasion, (or)
c) Pretreatment biopsy Gleason score ≥ 7 and extraprostatic extension with positive surgical margins in prostatectomy specimen.

Note: Patients treated with androgen ablation prior to surgery will have the pre-treatment biopsy reviewed. The Gleason score from the biopsy will be the one considered for inclusion in the study.

For patients without prior androgen ablation:

a) Gleason grade sum score ≥ 8 on radical prostatectomy specimen, (or)
b) Seminal vesicle invasion regardless of grade, (or)
c) Extraprostatic extension and positive surgical margins and Gleason sum ≥ 7.

4.1.5 Radical prostatectomy performed within 90 days of enrollment and serum PSA level < 0.1ng/ml prior to enrollment.

Please Note:
Some laboratories only report a value as low as 0.2 ng/ml. Therefore, they consider a value of less than 0.2ng/ml as undetectable. Only PSA values of less than 0.1ng/ml will be considered undetectable for this study. Some laboratories have agreed to send out serum samples to labs that offer a lower level of sensitivity. For example, Quest laboratory has agreed to send the samples to Dianon for an ultrasensitive PSA assay. This is easily performed by writing "Ultrasensitive PSA by Dianon- test code #36448" on the Quest requisition. Please check with your local lab to determine their lower limit of sensitivity for the serum PSA assay.

i. Written informed consent

ii. Criteria for Participating Urologists
Only those urologists who have completed at least a one year clinical fellowship in urologic oncology (certificate must be on file) may accrue patients to this study.

4.2. Substudy on wives'/partners' quality of life

4.2.1 Must have been in an intimate relationship with the trial participant for at least 2 years prior to the participant's enrollment in the clinical trial.

4.2.2 Must be female.

4.2.3 Verbally consents to participate in the partner QOL substudy.

5.0 Exclusion Criteria

5.1 Any evidence of metastatic disease confirmed prior to enrollment.

5.2 Inability to confirm pathologic risk factors or inadequate prostatectomy (see item 4.1.5).

5.3 Hormonal ablation for greater than 3 months or radiotherapy for prostate cancer.

5.4 Failure to achieve prostate specific antigen level of less than 0.1ng/ml prior to enrollment in study.

5.5 Elevation of liver function tests 2x normal.

5.6 Contraindication to the use of LH-RH agonists or antiandrogens.

5.7 Active secondary malignancy (other than squamous or basal cell skin cancer) within five years prior to enrollment in study.

5.8 Any concomitant medical condition that would make it undesirable for the patient to participate in the trial or jeopardize compliance with the protocol.

6.0 Pretreatment Evaluation

b. Complete history and physical examination within 90 days of enrollment.

c. Liver function tests (i.e. total bilirubin, AST, ALT, ALK phosphatase), PSA, prothrombin time (if on Coumadin) within days 90 of enrollment.

d. Specimen for Research

Specimen Preparation: Labeling and Submission

- One red top (10cc) tube is needed
- 10cc of blood is drawn from the patient and placed in a red top tube.
- Blood is allowed to clot.
- Centrifuge for 15 minutes to separate serum cells.
- Transfer a minimum of 1.0 cc of serum to a polypropylene vial.
- Label the sample with the patient I. D., study number, date drawn, and label the tube “research specimen”.
- Immediately freeze at –70 degrees C. Serum samples may be saved and sent in batches as long as they are maintained at – 70 degrees C. The samples must be mailed to the MDACC DMC within 1 year of registration.
- Complete the specimen transmittal form. One original must accompany the specimen. A copy is submitted as general data submission.

- Plan mailing so that the specimens do not arrive after 2:00 p.m. (CST) Monday through Friday and not on Saturday or Sunday and/or MDACC holidays.
- Mail the specimen on dry ice via overnight express (Federal Express or UPS) to:

THE UNIVERSITY OF TEXAS
M. D. ANDERSON CANCER CENTER
DATA MANAGEMENT CENTER
1100 HOLCOMBE BLVD. – ROOM 3.100
HOUSTON, TEXAS 77030

- The specimen must be packaged to avoid breakage, spillage, and other contamination.
- For specimen submission questions, call the MDACC Data Management Center at 713/792-8519.
- These specimens will be sent by the MDACC DMC to the Tumor Marker Lab room B4.4351 for processing and storage.

e. Bone scan- required if PSA>10 ng/ml prior to surgery. If not performed preoperatively must obtain prior to enrollment (< 90 days post surgery).

f. Pathology consult from M. D. Anderson Cancer Center study pathologist (if surgery performed elsewhere).

g. Patient quality of life measures – Dr. Basen-Engquist and staff of the MDACC Department of Behavioral Science will conduct a telephone interview after registration and before treatment with the patient that includes Medical Outcomes Study 36-Item. Short Form Health Survey (SF-36) (37), the Profile of Mood States (POMS) (38), UCLA Sexual Functioning Scale (39), the Dyadic Adjustment Scale (40), and the Southwest Oncology Group (SWOG) Treatment Specific Symptom Checklist. Patient preference data will also be collected at this time. Psychometric information about these questionnaires is provided in Appendix B.

h. Wife/partner quality of life measures –Dr. Basen-Engquist and staff of the MDACC Department of Behavioral Sciences will conduct a telephone interview after registration and before treatment with the wife/partner that includes Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (37), the Profile of Mood States (POMS) (38), UCLA Sexual Functioning Scale (adapted) (39), the Dyadic Adjustment Scale (40).

2. Registration/Randomization Procedure

7.1 All Extramural Collaborators will register patients by calling the MDACC Data Management Center between 8 am – 5 pm CST, Monday-Friday. This will allow the MDACC DMC to input these institutions and physicians into the computerized database. IRB approval will be verified and the eligibility checklist will be reviewed. A confirmation of registration and a reminder letter to forward pathology slides will be mailed to the Extramural Collaborator. A copy of the registration confirmation will be forwarded to the Department of Behavioral Science with the telephone number of the patient by the MDACC DMC.

7.2 After the pathology slides have been sent to the MDACC DMC and confirmed to be appropriate for randomization by the MDACC pathologist, the registering institution will be notified as to the patient's eligibility for randomization by the MDACC DMC. A patient may be randomized up to 3 weeks after registration. All Extramural at (713) 792-8519 between 8 am – 5 pm CST, Monday-Friday. A randomization checklist will be reviewed and patients will be stratified by the following criteria:

MDACC participants	vs	Extramural Collaborators
Pathologic Stage:		
Organ confined	vs	Other
Seminal vesicle	vs	Other
Margin status:		
Positive	vs	Negative
Pre prostatectomy PSA level:		
PSA ≤ 10 ng/ml	vs	PSA > 10 ng/ml
Neoadjuvant Hormonal Therapy	vs	None

A confirmation of randomization letter will be mailed to the participating institution/affiliate or Extramural Collaborators**.** Therapy must start within 10 days of randomization.

8.0 Treatment Plan

Subsequent to pretreatment evaluation and randomization, patients on arm A receive Goserelin 10.8 mg sc every 12 weeks (+/- 1 week) in addition to Bicalutamide 50 mg daily. The total treatment period for patients on Arm A will be one year. Patients on Arm B receive no initial treatment. At the time of relapse, patients in Study Arms A and B will receive additional therapy according to the clinical judgment of their physicians

Arm A - 165 patients - Goserelin + Bicalutamide (one year)

Arm B - 165 patients - No initial treatment

Treatment at relapse - Physician preference

9.0 Evaluation During Study (See Treatment Plan)

a. Arm A - Liver test 1, 2, 3, 6, 9, 12 months after initiating therapy. Solicitation of adverse events, physical examination, serum PSA, every three months (3-12 mos; +/- 2 weeks). Serum PSA, with physical examination every 6 months (mos. 13-60; +/- 1 month). Then yearly serum PSA and physical examination (> 60 mos. - 120 mos; +/- 1 month) or until biochemical or clinical progression. Patient's requiring Coumadin anticoagulation will have prothrombin time monitored at least every 3 months (+/- 2 weeks) and as necessary to adjust medication. For patients exhibiting disease progression (at anytime during study), physical examination and serum PSA tests will occur at a minimum of 12 month (+/- 1 month) intervals for the duration of the study (see section 10.0 also).

   Arm B - Liver function tests are not required for patients that are not receiving antiandrogen therapy. All other testing procedures and intervals are the same as Arm A.

b. Imaging studies will be obtained as clinically indicated.

c. Quality of life will be assessed by the SF-36 questionnaire (37), the POMS (38), the UCLA Sexual Functioning Scale (39), the Dyadic Adjustment Scale (40), and the Southwest Oncology Group Treatment Specific Symptoms checklist. Quality of life will be assessed at entry into the study as well as at 6 month intervals during years one and two of the study, and at one year intervals up until month 60. Quality of life questionnaire data will be collected by telephone interview. The interviews will last approximately 30-40 minutes. Before the interview takes place, we will contact patients to schedule a time for the interview. We also will send a copy of the interview questionnaire for patients to refer to during the interview. Patients will receive a small gift (worth about $10) for each quality of life interview they complete.

   In order to include Spanish speaking patients and their wives/partners in the QOL companion study, we will use Spanish versions of those questionnaires that have been translated, translate the questionnaires for which translations do not exist. The method for translation will include translating the questionnaire from English to Spanish, then having a different translator translate from Spanish back to English to determine if the appropriate meaning has been maintained. The translated questionnaire also will be reviewed and pilot-tested by Spanish-speaking individuals in focus groups.

   All quality of life data will be collected by M. D. Anderson personnel.

d. Wives/partners of trial participants will complete quality of life assessments every six months for the first two years of the study. The names and contact information of the wives/partners will be obtained from the patient when his baseline QOL interview is scheduled. Within three weeks of their husband's

enrollment in the trial, we will send a letter to the wives/partners explaining the purpose of the trial and what data will be collected. This will be followed by a telephone call in which we will reiterate the information supplied in the letter, obtain their verbal consent, and schedule the first telephone interview. The subsequent data will be collected using telephone interviews as well. Wives/partners of the trial participants will complete the same instruments as the trial participants, with two exceptions. They will not complete the treatment-related symptoms checklist, and they will complete a modification of the UCLA Sexual Functioning scale that excludes the items about erections. The women will receive a small gift (worth about $10) for each interview they complete. The data collection for the wives/partners substudy will be done by M. D. Anderson personnel.

10.0 Criteria For Progression

10.1 Criteria

a. Two successive rises in serum PSA beginning at a threshold value of 0.1 ng/ml or any single value ≥ 0.5 ng/ml. For PSA values between 0.1-0.4 ng/ml serum levels should be repeated at 3-month intervals to document the detectable level and to confirm a second rise. The date of documentation of the second increase is the recorded date of progression. For patients presenting with an initial PSA increase of ≥ 0.5 ng/ml, a repeat serum PSA level should be obtained prior to one month to confirm and document progression. The date of confirmation is the recorded date of progression.

b. In absence of above, biopsy proven recurrence.

10.2 Evaluation of disease recurrence

Subsequent to documentation of a rising PSA by the above criteria and prior to the institution of primary (Arm B patients at relapse) or secondary therapy (Arm A patients), patients **may** undergo **some of** the following evaluations **as** determined by the attending physician as clinically indicated:*

a. complete history and physical examination
b. bone scan
c. CT scan or MRI of abdomen and pelvis
d. transrectal ultrasound with biopsies of suspicious areas as well as the urethrovesical anastomosis

*Represents suggested disease evaluation- other tests should be ordered as clinically indicated.

11.0 Criteria for Removal from Study

11.1 Patient request

The patient gives verbal and/or written notification declining further participation in the study. The patient will be taken off study and data will be censored after the last follow up.

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11.2 Lost to Follow Up

The patient will be considered lost to follow up when a scheduled study follow up is missed and the patient cannot be contacted via a minimum of one certified letter and two telephone calls. If there is no response to certified mail within one month of the mailing date and the telephone calls are unanswered, the patient will be taken off study. Their data will be censored after the last documented follow up.

12.0 Protocol Deviation*

12.1 Noncompliance with medication (arm A). The use of non protocol compounds known to affect serum testosterone levels or have antiandrogenic action (arm A, B, i.e., finasteride, Saw Palmetto, etc.) prior to objective evidence of failure

12.2 Use of nonprotocol adjuvant therapies (i.e., radiation) prior to evidence of progression.

12.3 +Adverse event requiring cessation of therapy (severe event or elevation of liver function tests 2x normal).

12.4 Investigator feels it is in patient's best interest to discontinue therapy.

* Patients in the above categories (12.1-12.4) will have protocol deviations noted in the database. It will state type of deviation, date of deviation, status of patient, and whether patient is on study or off study. They will be followed throughout the course of the study and data will be analyzed on an intent to treat basis as well as a secondary analysis as to the actual treatment received.

+Patients requiring the discontinuation of bicalutamide due to elevation of liver function tests or inability to tolerate the antiandrogen (due to nausea or diarrhea) will be offered other commercially available antiandrogens. Alternatively, should they refuse they may continue on study receiving a LH-RH agonist as monotherapy.

13.0 Statistical Considerations

13.1 Objective 1.1

Recent series have reported 5 year disease free survival ranging from 44-68% among cohorts of patients with Gleason $\geq$ 8 prostate cancer, seminal vesicle invasion, or those with Gleason score 7 prostate cancer and extraprostatic extension of cancer with positive surgical margins (17-19). Considering the heterogeneity of results, we have assumed that patients randomized to arm B have at least a 35% rate of clinical or biochemical progression over five years. We

hypothesize that patients treated in an adjuvant setting (arm A) will exhibit a decrease in the recurrence rate to 20% over the same time period. To detect this 15% difference with a $p < 0.05$ and a statistical power of 90%, approximately 150 patients would need to be entered on each arm of the study (ST PLAN software). To account for a 10% drop-out rate, 30 additional patients would be randomized. Thus, 330 patients are anticipated to be randomized on this study. Results will be analyzed on an intent to treat basis and stratified for patients enrolled at M. D. Anderson versus extramural sites. In addition, patients will be stratified for the following Pathologic factors: pathologic stage - organ confined versus other, seminal vesicle involvement versus other, Margin status - positive versus negative Pre-prostatectomy PSA level ≤10 ng/ml versus >10 ng/ml. Data will be analyzed according to Kaplan-Meier/Cox methodology stratifying for the above variables. A separate analysis for efficacy and safety will be performed for patients treated with bicalutamide and lueprolide versus those receiving flutamide and lueprolide.

Although not specified as objectives of the study, patients will be followed for ten years to determine the incidence of androgen independent disease, disease specific, and overall. The study assumes that 33 of 165 patients randomized to Arm A, and 58 of 165 patients randomized to Arm B will fail within five years. Patients exhibiting clinical or biochemical evidence of failure will eventually be treated with hormonal ablative agents in an attempt to control the disease. The study assumes that other treatments could also be utilized (local radiation) by treating physicians, but that no curative therapy will become available during the study. In addition, the study assumes that the distribution of treatments between study arms will be similar. Thus the study would continue to have the power to detect a 15% difference between either study arm A or B for these endpoints with 90% power if the intercurrent death and drop-out rate does not exceed 10%. The study retains an 80% power to detect such a difference as long as the incidence of death from other causes or patient drop out does not exceed 35%.

13.2 Objective 1.2-1.3

Primary quality of life outcomes of this study are patient scores on the five quality of life measures, including physical function, emotional well-being, fatigue, sexuality, and treatment-specific symptoms. We will test for differences in the quality of life measures between the two patient groups using two-sided t-tests. Since there are five quality of life measures, the level of each test will be adjusted using a Bonferroni correction to preserve an overall type I error rate of 0.05 at each follow-up time point. For each test we will therefore use a level of $\alpha = 0.01$ (i.e., 0.01 = 0.05/5). To estimate power, we will use what Cohen (74) called an "effect size index," in which the detectable difference between two groups is given in terms of the population standard deviation units. For example, an effect size index of 0.25 represents a detectable difference between two groups equal to 0.25 standard deviation units. Assuming that the quality of life companion study will have a higher dropout rate than the clinical trial (15% rather than 10%) we are estimating that 174 patients per treatment arm would be available for the quality of life analysis. At a level of $\alpha = 0.01$, we will have 80% power to detect a difference of 0.37 standard deviation units. Given the assumption that 76% of the

men enrolling in the study will be married or have steady partners (based on census data) and that 80% of the partners will participate in the study, we estimate that 132 wives/partners will be included in each study arm. At a level of $\alpha = 0.01$, we will have 80% power to detect a difference of 0.43 standard deviation units. Cohen (74) describes effect size values of 0.25 as being "small," values of 0.50 as being "medium," and values of 0.80 as being "large."

13.2.1 Statistical analyses of primary quality of life hypotheses

- Hypothesis 1.1: A significant treatment arm-by-time interaction will be found, indicating that the quality of life of patients in the androgen ablation arm will be poorer than that of the control arm patients during and shortly after androgen ablation, and but better than patients in the control arm at the 2 to 5 year assessments.
- Hypothesis 1.2: A significant treatment arm-by-time interaction will be found, indicating that the quality of life of wives/partners of patients in androgen ablation arm will be poorer than that of the wives/partners of control arm patients during and shortly after patients' androgen ablation, but better than wives/partners of patients in the control arm at the 2 year assessment.

Descriptive statistics (e.g., means, ranges, standard deviations) will be computed for the quality of life scores at each time point for each of the two groups. Ninety-five percent confidence intervals will be constructed for each of the means. Graphic methods (e.g., boxplots and histograms) will also be employed to closely examine the distributions of the quality of life scores at each time point. Bivariate associations between quality of life and selected demographic and disease-related variables, including age, socioeconomic status, ethnicity, time since diagnosis, and duration of treatment will be evaluated using Pearson's product-moment correlation coefficients together with scatterplots where appropriate.

We will test for differences in the quality of life measures between the two patient groups using two-sided *t*-tests at $\alpha = 0.01$ to preserve the overall type I error rate of $\alpha = 0.05$. Although the randomization procedure insures the validity of the *t*-tests, additional analyses will be conducted using linear regression analyses. In these analyses, each quality of life measure will be regressed onto treatment condition and several potential confounders, including baseline quality of life, age, ethnicity, and socioeconomic status. Potential pairwise interactions between the treatment condition and the confounders also will be evaluated. This portion of the modeling allows us to explore whether the treatment affects certain groups of participants' quality of life more than it does others'. However, since these analyses involve considerable exploratory modeling, results will be interpreted as hypothesis generating. Relevant regression model assumptions will be evaluated using standard residual-based methods, and corrective measures such as normalizing transformations will be made as appropriate (75).

We also will evaluate differences in quality of life using a more global approach developed by O'Brien (76) and proposed for use in quality of life studies by Tandon (77). In this analysis, the group differences in the individual quality of life dimensions will be combined using a weighted sum of the individual test

statistics, with the weights chosen from the observed covariance matrix. This summary statistic can then be used to test whether an overall difference exists between the two treatment groups with respect to the quality of life scales.

We expect that the differences in quality of life at the follow-up periods will change over time. Therefore, we will also attempt to formally characterize any pattern of change in quality of life using linear regression with a quadratic term in time. This will allow us to model reasonably smooth departures in time from strictly straight-line trends. Interactions between the treatment group variable and time will indicate differing linear or quadratic trends in quality of life for the two treatment groups and will reveal whether the quality of life scores converge in time. In order to preserve the overall type I error rate of 0.05, the interaction terms will also be tested at $\alpha = 0.01$ for the individual quality of life scores. Since a patient will contribute quality of life scores at several time points, the scores within each individual will be correlated. We will use the Generalized Estimating Equation (GEE) methodology to fit the regression models (78). GEE provides regression parameter estimates that have interpretations identical to those of standard linear regression methods. The GEE models differ in that the standard error estimates of the regression coefficients are inflated to account for the observed correlation in the data. One significant advantage of GEE is that data from all patients can be incorporated into the analyses. For example, patients who contribute follow-up quality of life scores only at the 6 month follow-up can be included with those who contribute quality of life scores at each follow-up time. This maximizes the potential power available at the conclusion of the trial for evaluating the treatment-by-time interaction. This approach to modeling patterns of change over time has been recently suggested for longitudinal quality of life data in a paper by Schumacher, Olschewski, and Schulger (79).

Similar analyses will be conducted to evaluate quality of life among the spouses.

13.2.2. Statistical Analysis of secondary quality of life hypotheses

Analysis of utilities

- Hypothesis 2.1a: Utilities will change over time (insufficient data available to predict direction of change)
- Hypothesis 2.1b: The severity/intensity o treatment-specific symptoms, weighted by the symptoms' utilities, will be correlated with a rating of general health perceptions.
- Hypothesis 2.1c: Utilities assessed by telephone and in face-to-face interviews will not differ (UTMDACC patients only).
- Hypothesis 2.1d: Utilities assessed by the time trade-off method will be significantly correlated with those assessed by a visual analog scale.
- Hypothesis 2.1e: The utility of "current health" will be related to quality of life indicators.

For Hypothesis 2.1a, we will use a similar approach to that described above to evaluate quality of life changes over time. Specifically, we will first conduct descriptive analyses to characterize the distributions of patient preferences at the different time points for the two groups. This will be followed by formally testing

the differences in patient preferences between the two groups using t-tests. Regression analyses using the GEE methodology will be used to specifically model the changes in patient preferences over time.

For Hypotheses 2.1b, 2.1d, and 2.1e we will use Pearson's Product Moment correlation coefficients to evaluate the respective hypotheses. We will use graphical methods including boxplots, histograms, and scatterplots to evaluate the distributional assumptions and use nonparametric rank correlations if necessary.

Finally, in testing Hypothesis 2.1c we will use linear regression. In this analysis, utilities will be regressed onto an indicator variable representing type of interview (telephone vs. face-to-face) together with potential confounders such as age and socioeconomic status. Confounders will be included in the equation if they significantly ($p < .05$) improve the fit of the model. Regression model assumptions will be evaluated as described above.

Because the analysis of the secondary hypotheses are considered largely exploratory, no adjustments will be made for multiple comparisons.

Mediation of treatment effect on quality of life

- Hypothesis 2.2: Treatment effects on quality of life will be mediated by treatment-specific symptoms and recurrence of disease.

We hypothesize that the effect of treatment on quality of life will be mediated by recurrence and/or treatment-specific symptoms. To evaluate whether these variables act as mediating variables between treatment and quality of life, we will use the criteria described by Baron and Kenny (80). Evidence of mediation for a particular variable would be indicated by (1) the treatment is related to the hypothesized mediating variable, (2) the mediating variable is related to quality of life, and (3) inclusion of the hypothesized mediating variable in the model reduces the direct effect of treatment on quality of life. The mediational hypothesis will be investigated for each of the quality of life indices. Three regression equations will be estimated to assess whether all specified criteria are met. For example, to test condition 1, the mediating variable will be regressed onto the treatment variable; we will assess whether differences in recurrence and treatment-specific symptoms results from differences in treatment group. If significant treatment effects are found, then we will proceed to determine if criteria 2 and 3 are satisfied.

We will use a structural equation modeling framework to evaluate the mediating effects of recurrence and treatment-specific symptoms individually and simultaneously. The structural equation modeling approach allows one to control for measurement error in the mediating variables, control for baseline quality of life, fit the entire mediational process rather than individual components, and use multiple mediators and multiple outcomes. The mediational hypothesis suggests that the indirect effect of the treatment variable on the quality of life indices through the mediators is statistically important, and inclusion of this indirect effect will reduce the direct effect of the treatment variable on quality of life. First, we will fit the model that accounts for the direct effects of the treatment variable to the mediator variables and quality of life measures. Then, the paths from the mediator variables to the quality of life measures will be included. The

change in chi-squared statistic will indicate whether the mediational paths are statistically important.

Interactive dyadic effects on quality of life

- Hypothesis 2.3a: Changes in the patient's quality of life will influence the spouse's quality of life.
- Hypothesis 2.3b: Changes in the spouse's quality of life will influence the patient's quality of life.
- Hypothesis 2.3c: The influence of each partner's quality of life on the quality of life of the other partner will be moderated by the couple's marital distress.

Sequential dyadic interaction models (68,81-82) will be used to evaluate the nature of the quality of life relational patterns between the patient and his wife. These models allow (a) measurements at multiple time points, (b) measurements of multiple quality of life variables, and (c) measurements of multiple attribute variables. The models predict the joint probability of patient's and spouse's quality of life responses at the six-month follow-up visit to be a function of their quality of life at baseline, and the joint probability of their quality of life responses at the 12-month follow-up to be a function of their quality of life at baseline and the six-month follow-up. The model will include parameters that reflect:

(1) Self-influences: the quality of life of each dyad member predicts that member's future quality of life.

(2) Reciprocity: the tendency for consensus on quality of life by patient and spouse at each time point.

(3) Direct dominance: the quality of life of one member of the dyad (e.g., patient) predicts the future quality of life of the other member (e.g., spouse).

(4) Indirect dominance: the quality of life of one member of the dyad (e.g., patient) predicts the future joint quality of life of the dyad pair.

The analysis will be conducted for each individual quality of life index. Following the univariate analyses, multiple indices will be examined to investigate more complex hypotheses, such as: (1) patient symptomatology influences the spouse's quality of life; and (2) the psychological well-being and sexual functioning of patient and spouse predict marital distress. Finally, the effect of treatment group on the level of reciprocity and dominance will be examined.

14.0 Data and Protocol Management

Protocol Study Oversight

The University of Texas M. D. Anderson Cancer Center (MDACC) Institutional Review Board (IRB) will provide oversight solely for study patients treated at

MDACC. Participating study sites that are part of the Linked Urology Research Network (LURN) will have study oversight provided by a central institutional review board. Other participating academic institutions (i.e., not MDACCC or LURN) should obtain IRB approval from their IRB who will oversee the study.

All patients entered from MDACC and participating sites will be registered by the MDACC Data Management Center (DMC) at (713) 792-8519. IRB approval will be verified and the eligibility checklist will be reviewed. No patient can be entered on protocol if they do not satisfy all eligibility requirements. Protocol specific forms will be utilized for data acquisition. Data will be monitored by the principal investigator every 3 months.

The MDACC Extramural Collaborators Procedures documents the data management and quality assurance programs for this collaboration.

Principal Investigators: The M.D. Anderson Principal Investigator will be responsible for the conduct of the study and monitoring its progress. The responsibility for all reports and forms required will be that of the principal investigator.

Procedures for Patient Entry: All Extramural Collaborators patients will be registered by the Data Management Center of the Department of Biostatistics at (713) 792-8519, from 8:00 a.m. – 5:00 p.m. (CST). The eligibility checklist will be faxed before registering/randomizing a patient. This office will then enter the patients on the Protocol Data Management Center (PDMS). All eligibility requirements will be checked prior to registration. No patient can be entered on protocol if they do not satisfy all eligibility requirements.

Data Management: All data will be entered in PDMS at MDACC. Data from Extramural Collaborators will be forwarded by hard copy. Protocol-specific forms are attached to this study for use by the Extramural Collaborators. All investigators will utilize these forms for onstudy, flowsheet, offstudy and toxicity data.

Data Monitoring: All CRF's will be monitored and collected by the MDACC DMC.

All submitted forms will be monitored by the MDACC research nurse specifically assigned to this protocol. Any major deficiencies will be corrected by telephone communication. All data forms will be monitored for completeness of data. Key parameters such as drug dosages including attenuations and escalations, adverse event documentation, and tumor measurements will analyzed.

The schedule for form submission is as follows:

On study form, Informed consent, Pathology, Flowsheet (#1) Eligibility Checklist	14 days after registration
Flowsheet interim evaluations	21 days after evaluation

Offstudy	14 days after offstudy date
Reportable adverse drug reaction	7 days after occurrence

Toxicity Surveillance: All major (Grade 4 and 5) or unexpected toxicities will be reported within 24 hours to the Data Management Center at (713) 792-8519. The principal investigator at MDACC will be responsible for communicating toxicity reactions.. All Extramural Collaborators reporting a major toxicity will submit a toxicity form within 7 days of the occurrence. All Grade 2-3 unknown reactions will be reported in writing within 7 working days.

The standard FDA Adverse Reaction Report (MedWatch) reporting form will be used for reporting toxicities and unknown reactions. The guidelines for reporting adverse drug reactions to MedWatch are outlined in the section entitled Reporting Requirements.

Quality Assurance: Quality assurance measures are provided by three mechanisms: ongoing monitoring of protocol compliance, on-site audits and response reviews. All data submitted to the Data Management Center will be monitored for timeliness of submission, completeness and adherence to protocol requirements. Monitoring will begin at the time of patient registration and will continue during protocol performance and completion. The MDACC Data Management Center research nurses will perform the on-going protocol compliance with the support of Extramural Data Management personnel.

All records, x-rays, and scans will be sent to Houston for confirmation of progression.

Drug Ordering: Drug to be supplied by AstraZeneca Pharmaceutical company to the M. D. Anderson Cancer Center Pharmacy for patients randomized to initial therapy (Arm A). Drug will be shipped from M. D. Anderson to Extramural Collaborators as necessary. Each institution will maintain its own drug logs in accordance with MedWatch requirements.

Institutional Review: Each Extramural Collaborator will submit the protocol to their own Institutional Review Board. Documentation of approval of the IRB will be forwarded to the MDACC Data Management Center - Box 501, 1515 Holcombe Blvd., Houston, Texas 77030 before a patient from that institution can be registered on protocol. No changes in the protocol will be allowed unless approved by the MDACC principal investigator. All IRBs will have an OPRR Assurance number.

Protocol Revisions and Closures:
Non life-threatening revisions: Extramural Collaborators will receive written notification of protocol revisions regarding non-life threatening events and will be given 7 days from receipt of the notification to implement the revision.

Life-threatening revisions: Extramural Collaborators will receive telephone notification of life-threatening revisions with follow up by mail. Life-threatening protocol revisions will be implemented immediately.

Protocol closures and temporary holds: Extramural Collaborators will receive telephone notification of protocol closures and temporary holds, with follow up by mail. Closures and holds will be effective immediately. Extramural Collaborators will be updated on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

14.1 Reporting Requirements

All patients will be monitored for adverse events occurring coincident to study drug administration. Adverse events will be recorded in the appropriate section of the case report form. Reports will include the nature of the incident, its severity, relationship to drug, date, and time of onset, duration, outcome and specific or symptomatic therapy. Events clearly related to treatment or unexpected life threatening toxicities will be reported immediately to MDACC DMC who in turn will notify the study chairman and the Surveillance Committee.

14.2 Quality of Life Data Management

Data management for the quality of life companion study will be done by the data management and analysis core in the department of behavioral science. Data collected by telephone interview will be entered directly into a computer using a Computer Assisted Telephone Interview (CATI) system. Data collected using in-person interviews will be entered using Access database software. Participant names will not be included in the data file. A participant's record in the data file will be identified by a study identification number only, and the file linking study identification numbers and names will be kept in a separate location. Only Dr. Basen-Engquist and the quality of life study coordinator will have access to this file.

Weekly and monthly backups will be made of all quality of life study data. The monthly back-up tapes will be stored in a fireproof safe.

15.0 Adverse Events and Reporting Requirements (M. D. Anderson patients)

All patients will be monitored for adverse events occurring coincident to study drug administration. Adverse events will be recorded in the appropriate section of the institutional case report form. Reports will include the nature of the incident, its severity, relationship to drug, date, and time of onset, duration, outcome and specific or symptomatic therapy. Events clearly related to treatment or unexpected life threatening toxicities will be reported immediately to the study chairman who, in turn, must notify the Surveillance Committee. The MedWatch reporting form will be used for reporting toxicities and unknown reactions.

<u>Unknown Toxicities</u>

1. Grade 2 - 3

    1. A standard FDA Adverse Reaction Report (Form 3500, MedWatch for commercial drugs) within 7 working days to MDACC Data Management Center.

    b. MDACC Data Management Center will forward ADR form to OPR and primary investigator to meet 10 day reporting deadline.

2. Grade 4 and 5

    a. Telephone MDACC Data Management Center at (713) 792-8519 within 24 hours to report toxicity.

    2. MDACC Data Management Center will telephone primary investigator immediately after receiving the Extramural Collaborator's call to report toxicity.

    3. Submit a Standard FDA Adverse Reaction Report Form 3500, MedWatch for commercial drugs) within 7 working days to MDACC Data Management Center.

    4. MDACC Data Management Center will forward ADR form to OPR and principal investigator to meet 10 days reporting deadline.

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Evaluation During Study-Flow Sheet

	Baseline within 90 days	1 mos.	2 mos.	3 mos.	6 mos.	9 mos.	12 mos.	18 mos.	24 mos.	25-60 mos.(4)	61-120 mos.(6)	
Complete History	X											
Physical Exam	X			X	X	X	X	X	X	X	X	
PSA	X			X	X	X	X	X	X	X	X	
Liver Function Tests(1)		X	X	X	X	X	X	X				
Prothrombin Time(2)	X			X	X	X	X					
Bone Scan(3)	X											
Pathology Consult	X											
QOL	X				X		X	X	X	X(5)		
Adverse Events/Interim Progress		X			X	X	X	X	X	X	X	X
Research Blood	X											

(1)Post randomization liver function tests only required on treatment arm

(2)Prothrombin time obtained every 3 months if on coumadin and receiving drug (Arm A)

(3)Required if PSA prior to surgery > 10 ng/ml

(4)Tests/visits every 6 months (+/- 1 months)

(5)QOL every 12 months (+/- 2 months)

(6)Tests/visits every 12 months (+/- 2 months)

Every 3 month follow up is (+/- 2 weeks)

Every 6 month follow up is (+/- 1 month)

Every 12 month follow up is (+/- 2 months)

Dyadic Adjustment Scale

DYADIC ADJUSTMENT SCALE

Most persons have disagreements in their relationships. Please indicate below the approximate extent of agreement or disagreement between you and your partner for each item on the following list.

	Always agree	Almost always agree	Occasionally disagree	Frequently disagree	Almost always disagree	Always disagree
1. Handling family finances.	5	4	3	2	1	0
2. Matters of recreation.	5	4	3	2	1	0
3. Religious matters.	5	4	3	2	1	0
4. Demonstrations of affection.	5	4	3	2	1	0
5. Friends.	5	4	3	2	1	0
6. Sex relations.	5	4	3	2	1	0
7. Conventionality (correct or proper behavior).	5	4	3	2	1	0
8. Philosophy of life.	5	4	3	2	1	0
9. Ways of dealing with parents or in-laws.	5	4	3	2	1	0
10. Aims, goals, and things believed important.	5	4	3	2	1	0
11. Amount of time spent together.	5	4	3	2	1	0
12. Making major decisions.	5	4	3	2	1	0
13. Household tasks.	5	4	3	2	1	0
14. Leisure-time interests and activities.	5	4	3	2	1	0
15. Career decisions.	5	4	3	2	1	0

	All of the time	Most of the time	More often than not	Occasionally	Rarely	Never
16. How often do you discuss or have you considered divorce, separation, or terminating your relationship?	0	1	2	3	4	5
17. How often do you or your mate leave the house after a fight?	0	1	2	3	4	5
18. In general, how often do you think that things between you and your partner are going well?	0	1	2	3	4	5
19. Do you confide in your mate?	0	1	2	3	4	5
20. Do you ever regret that you married (lived together)?	0	1	2	3	4	5
21. How often do you and your partner quarrel?	0	1	2	3	4	5
22. How often do you and your mate “get on each other’s nerves”?	0	1	2	3	4	5

	Every day	Almost every day	Occasionally	Rarely	Never
23. Do you kiss your mate?	4	3	2	1	0

	All of them	Most of them	Some of them	Very few of them	None of them
24. Do you and your mate engage in outside interests together?	4	3	2	1	0

How often would you say the following occur between you and your mate:

	Never	Less than once a month	Once or twice a month	Once or twice a week	Once a day	More often
25. Have a stimulating exchange of ideas.	0	1	2	3	4	5
26. Laugh together.	0	1	2	3	4	5
27. Calmly discuss something.	0	1	2	3	4	5
28. Work together on a project.	0	1	2	3	4	5

These are some things about which couples sometimes agree and sometimes disagree. Indicate if either item below caused differences of opinions or were problems in your relationship during the past few weeks.

	Yes	No	
29.	0	1	Being too tired for sex.
30.	0	1	Not showing love.

31. The following words represent different degrees of happiness in your relationship. The word, “happy,” represents the degree of happiness of most relationships. Please tell us which word best describes the degree of happiness, all things considered, in your relationship.

0	1	2	3	4	5	6
Extremely unhappy	Fairly unhappy	A little unhappy	Happy	Very happy	Extremely happy	Perfect

32. Which of the following statements best describes how you feel about the future of your relationship:

5 I want desperately for my relationship to succeed and would go to almost any lengths to see that it does.

4 I want very much for my relationship to succeed and will do all that I can to see that it does.

3 I want very much for my relationship to succeed and will do my fair share to see that it does.

2 It would be nice if my relationship succeeded, but I can't do much more than I am doing now to help it succeed.

1 It would be nice if it succeeded, but I refuse to do any more than I am doing now to keep the relationship going.

0 My relationship can never succeed, and there is no more that I can do to keep the relationship going.

Profile of Mood States (POMS)

Below are words that describe feelings and moods people have. Please read EVERY word carefully. Then fill in ONE space under the answer which best describes how you feel RIGHT NOW (that is, at the present moment).

Suppose the word is *happy*. Mark the one answer which is closest to how you feel RIGHT NOW (that is, at the present moment).

	0	=	Much unlike this
The numbers refer	1	=	Slightly unlike this
to these phrases.	2	=	Slightly like this
	3	=	Much like this

	Much Unlike This	Slightly Unlike This	Slightly Like This	Much Like This
1. Composed.....	0	1	2	3
2. Angry.....	0	1	2	3
3. Cheerful.....	0	1	2	3
4. Weak.....	0	1	2	3
5. Tense.....	0	1	2	3
6. Confused.....	0	1	2	3
7. Lively.....	0	1	2	3
8. Sad.....	0	1	2	3
9. Friendly.....	0	1	2	3
10. Tired.....	0	1	2	3
11. Strong.....	0	1	2	3
12. Clearheaded.....	0	1	2	3
13. Untroubled.....	0	1	2	3
14. Grouchy.....	0	1	2	3
15. Playful.....	0	1	2	3
16. Timid.....	0	1	2	3
17. Nervous.....	0	1	2	3
18. Mixed-up.....	0	1	2	3
19. Vigorous.....	0	1	2	3
20. Dejected.....	0	1	2	3
21. Kindly.....	0	1	2	3
22. Fatigued.....	0	1	2	3
23. Bold.....	0	1	2	3
24. Efficient.....	0	1	2	3
25. Peaceful.....	0	1	2	3
26. Furious.....	0	1	2	3
27. Lighthearted.....	0	1	2	3
	Much Unlike This	Slightly Unlike This	Slightly Like This	Much Like This
28. Unsure.....	0	1	2	3

29. Jittery.....	0	1	2	3
30. Bewildered.....	0	1	2	3
31. Energetic.....	0	1	2	3
32. Lonely.....	0	1	2	3
33. Sympathetic.....	0	1	2	3
34. Exhausted.....	0	1	2	3
35. Powerful.....	0	1	2	3
36. Attentive.....	0	1	2	3
37. Serene.....	0	1	2	3
38. Bad tempered.....	0	1	2	3
39. Joyful.....	0	1	2	3
40. Self-doubting.....	0	1	2	3
41. Shaky.....	0	1	2	3
42. Perplexed.....	0	1	2	3
43. Active.....	0	1	2	3
44. Downhearted.....	0	1	2	3
45. Agreeable.....	0	1	2	3
46. Sluggish.....	0	1	2	3
47. Forceful.....	0	1	2	3
48. Able to concentrate.....	0	1	2	3
49. Calm.....	0	1	2	3
50. Mad.....	0	1	2	3
51. Jolly.....	0	1	2	3
52. Uncertain.....	0	1	2	3
53. Anxious.....	0	1	2	3
54. Muddled.....	0	1	2	3
55. Ready-to-go.....	0	1	2	3
56. Discouraged.....	0	1	2	3
57. Good-natured.....	0	1	2	3
58. Weary.....	0	1	2	3
59. Confident.....	0	1	2	3
60. Businesslike.....	0	1	2	3
61. Relaxed.....	0	1	2	3
62. Annoyed.....	0	1	2	3
	Much Unlike This	Slightly Unlike This	Slightly Like This	Much Like This
63. Elated.....	0	1	2	3

64. Inadequate.....	0	1	2	3
65. Uneasy.....	0	1	2	3
66. Dazed.....	0	1	2	3
67. Full of pep.....	0	1	2	3
68. Gloomy.....	0	1	2	3
69. Affectionate.....	0	1	2	3
70. Drowsy.....	0	1	2	3
71. Self-assured.....	0	1	2	3
72. Mentally alert.....	0	1	2	3

Medical Outcomes Study
36-Item Short Form Health Survey (SF-36)

1. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(Circle 1, 2, or 3 on each line)

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.....	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	1	2	3
c. Lifting or carrying groceries.....	1	2	3
d. Climbing **several** flights of stairs.....	1	2	3
e. Climbing **one** flight of stairs.....	1	2	3
f. Bending, kneeling, or stooping.....	1	2	3
g. Walking **more than a mile**.....	1	2	3
h. Walking **several blocks**.....	1	2	3
i.. Walking **one block**.....	1	2	3
j. Bathing or dressing yourself.....	1	2	3

2. During the PAST 4 WEEKS, have you had any of the following problems with your work or other regular daily activity as a resutl of your **PHYSICAL HEALTH**?

(Please answer YES or NO for each question by circling 1 or 2 on each line.)

	Yes	No
a. Cut down the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort	1	2

3. During the **PAST 4 WEEKS**, have you had any of the following problems with your work or other regular daily activities as a result of your **EMOTIONAL PROBLEMS**, such as feeling depressed or anxious?

(Please answer YES or NO for each question by circling 1 or 2 on each line.)

	Yes	No
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

4. These questions are about how you feel and how things have been with you **during the PAST 4 WEEKS**. For each questions, please give the one answer that comes closest to the way you have been feeling.
How much of the time **during the past 4 weeks**...

(Circle one number on each line.)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

5. During the **past 4 weeks,** how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	1	
Most of the time.....	2	
Some of the time.....	3	(Circle one number)
A little of the time.....	4	
None of the time.....	5	

6. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with friends, friend, neighbors, or groups)?

Not at all.....	1	
Slightly.....	2	
Moderately.....	3	(Circle one number)
Quite a bit	4	
Extremely.....	5	

7. How much **bodily** pain have you had during the **past 4 weeks**?

None.....	1	
Very mild.....	2	
Mild.....	3	(Circle one number)
Moderate.....	4	
Severe.....	5	
Very severe.....	6	

8. During the **past 4 weeks,** how much **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all.....	1	
Slightly.....	2	
Moderately....	3	(Circle one number)
Quite a	4	
Extremely.....	5	

9. Please choose the answer that best describes how true or false each of the following statements is for you.

(Circle one number on each line.)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier	1	2	3	4	5
b. I am as healthy as anyone I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

10. In general, would you say your health is:

Excellent.....	1	
Very Good.....	2	
Good.....	3	(Circle one number)
Fair.....	4	
Poor.....	5	

11. **Compared to one year ago**, how would you rate your health in general **now**?

Much better now than one year ago.....	1	
Somewhat better now than one year ago.....	2	
About the me.....	3	(Circle one number)
Somewhat worse now than one year ago.....	4	
Much worse now than one year ago.....	5	

Southwest Oncology Group Treatment Specific Symptom Scale

TREATMENT-SPECIFIC SYMPTOMS

The following items describe symptoms that are common for people undergoing treatment for prostate cancer. Please circle one number for each item and make your choice with respect to the last week.

32. **DIARRHEA**

1 I seldom have more than two normal stools per day
2 I have occasional diarrhea (two or three loose stools per day, no more than once a week)
3 I have fairly frequent diarrhea (two or three loose stools per day several times a week)
4 I have frequent diarrhea (two or three loose or watery stools daily)
5 I have more than three watery stools daily
6 I have had a colostomy

33. **CRAMPY, ABDOMINAL PAIN**

1 I seldom if ever have crampy, abdominal pain
2 I have occasional crampy, abdominal pain (no more than once a week)
3 I have fairly frequent crampy, abdominal pain (several times a week)
4 I have frequent crampy, abdominal pain (once a day)
5 I have crampy, abdominal pain several times a day

34. **TENDERNESS AND URGENCY WITH BOWEL MOVEMENTS**

1 My bowel movements are normal
2 I have occasional mild urgency to move my bowels or tenderness with bowel movement (no more than once a week)
3 I have fairly frequent mild urgency or tenderness with my bowel movements (several times a week)
4 I have mild to moderate urgency, pain and occasional mild bleeding with bowel movements (no more than twice a week)
5 I have frequent severe urgency, pain or bleeding with bowel movements
6 I have had a colostomy

35. **URINE FLOW**

1 My urine flows easily
2 My urine flows fairly easily
3 My urine flows slowly but I don't have to strain or bear down to empty my bladder
4 My urine flows very slowly and I have to strain or bear down to empty my bladder
5 My urine flows very slowly and I have to strain or bear down a great deal to empty my bladder
6 I have an indwelling catheter

36. In the past week did you:

1 Have <u>total control</u> over your urine flow
2 Have problems with dribbling, but not all the time or only at certain times of the day
3 Have a lot of problems with dribbling
4 Lose larger amounts of urine than dribbling but not all day long
5 Have <u>no control</u> over your urine flow (that is, you were totally incontinent)
6 I have an indwelling catheter

37. In the past week, I tended to urinate

1 4 or less times a day
2 5 to 8 times a day
3 9 to 12 times a day
4 More than 12 times a day
5 I have an indwelling catheter

38. **GAS PAIN**
1. I seldom if ever feel bloated or have gas pain
2. I have occasional gas pain (no more than once a week)
3. I have fairly frequent gas pain (several times a week)
4. I have frequent gas pain (once a day)
5. I have gas pain several times a day

39. **HOT FLASHES**
1. I seldom if ever have hot flashes
2. I have occasional hot flashes (several times a month)
3. I have fairly frequent hot flashes (once a week)
4. I have frequent hot flashes(several times a week)
5. I have hot flashes several times a day

40. **BREAST TENDERNESS**
1. I do not have a problem with breast tenderness
2. I have some breast tenderness but it doesn't bother me
3. I have breast tenderness that bothers me somewhat
4. I have breast tenderness that bothers me a great deal
5. My breast tenderness is unbearable

41. **BREAST SWELLING/ENLARGEMENT**
1. I do not have a problem with breast swelling
2. I have some breast swelling but it doesn't bother me
3. I have breast swelling that bothers me somewhat
4. I have breast swelling that bothers me a great deal
5. My breast swelling is totally unacceptable to me

UCLA Sexual Functioning Scale

SEXUAL FUNCTION

The next section is about your sexual function and sexual satisfaction. many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, YOUR NAME DOES NOT APPEAR ANYWHERE ON THIS SURVEY. Please answer honestly about **THE LAST 4 WEEKS ONLY.**

1. How would you rate each of the following during the last 4 weeks?
(Circle Yes/No)

	Very Poor	Poor	Fair	Good	Very Good
a. Your level of sexual desire?.....	1	2	3	4	5
b. Your ability to have an erection?.....	1	2	3	4	5
c. Your ability to reach orgasm (climax)?.....	1	2	3	4	5

2. How would you describe the usual QUALITY of your erections?

None at all.....	1	
Not firm enough for any sexual activity.....	2	
Firm enough for masturbation and foreplay only.....	3	(Circle one number)
Firm enough for intercourse.....	4	

3. How would you describe the FREQUENCY of your erections?

I NEVER had an erection when I wanted one.....	1	
I had an erection LESS THAN HALF the time I wanted one..	2	
I had an erection ABOUT HALF the time I wanted one.....	3	(Circle one number)
I had an erection MORE THAN HALF the time I wanted one	4	
I had an erection WHENEVER I wanted one.....	5	

4. How often have you awakened in the morning or night with an erection?

Never.....	1	
Seldom (less than 25% of the time).....	2	
Not often (less than half the time).....	3	(Circle one number
Often (more than half the time).....	4	
Very often (more than 75% of the time).....	5	

5. During the last 4 weeks did you have vaginal or anal intercourse ?

No.....	1	
Yes, Once.....	2	(Circle one number)
Yes, More than Once.....	3	

6. Overall, how would you rate your ability to function sexually during the last 4 weeks?

Very poor.....	1	
Poor.....	2	
Fair.....	3	(Circle one number)
Good.....	4	
Very good.....	5	

7. Overall, how big a problem has your sexual function been for you during the last 4 weeks?

No problem.....	1	
Very small problem.....	2	
Small problem.....	3	(Circle one number)
Moderate problem.....	4	
Big problem.....	5	

Psychometric information on quality of life questionnaires

The quality of life measures to be used are frequently used instruments whose reliability and validity have been tested. Normative data are available for most of the measures, permitting comparisons of the scores obtained with samples of individuals from the general population.

Medical Outcomes Study (SF-36) Health Survey

The SF-36 is a measure of general quality of life. In a sample of patients with chronic medical and psychiatric conditions, internal consistency reliability coefficients were high for its eight scales: physical function (0.93), social function (0.85), bodily pain (0.82), emotional well-being (0.90), vitality (0.87), general health perceptions (0.78), role limitations due to physical problems (0.84), and role limitations due to emotional problems (0.83) (26). The SF-36 was designed for self, telephone, and interviewer administration.

The SF-36 has been used in several studies of prostate cancer patients' quality of life (28,79). In a sample of 308 men receiving treatment for prostate cancer, internal consistency reliability coefficients for the eight scales were all greater than 0.80 (80).

Profile of Mood States

The Profile of Mood States (POMS) is included to provide a more comprehensive measure of emotional distress than the emotional well-being subscale of the SF-36. The POMS includes 65 questions measuring six mood states: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. In a study of 350 male psychiatric outpatients, the internal consistency reliability for these states were: tension (0.92), depression (0.95), anger (0.92), vigor (0.89), fatigue (0.94), and confusion (0.87). In a sample of 650 female psychiatric outpatients, the internal consistency reliabilities were: tension (0.90), depression (0.95), anger (0.93), vigor (0.87), fatigue (0.93), and confusion (0.84). Using this same data, a short version of the POMS was developed that consists of 30 items and the same six scales measured by the long form. The internal consistency reliabilities for the short form ranged from 0.75 (confusion) to 0.90 (vigor) for females and 0.79 (confusion) to 0.91 (fatigue) for males (27). The long form of the POMS has been used in studies evaluating the effects of treatment of prostate cancer (36,81) and to assess the emotional state of men with testicular cancer (82-84). In our pilot test, we will assess the reliability of the short form scales and the correlation of scores from the short and long versions of the POMS to determine if the short form is appropriate for our use.

Southwest Oncology Group Treatment Specific Symptom Scale

This scale was developed specifically to measure symptoms of patients receiving androgen ablation treatment for prostate cancer. It includes single items to measure diarrhea, abdominal pain, bowel function, gas pain, hot flashes, breast tenderness, and breast swelling; three items measure urine flow. Because items have not been summed to create an overall scale, but are scored separately, estimates of internal consistency reliability are not available (Carol Moinpour, Ph.D., personal communication, 1997). This scale was used in a study to assess treatment-related symptoms after nerve-sparing radical prostatectomy for early (non-metastatic) prostate cancer (85). The scale also is being used in a SWOG study of intermittent androgen deprivation in patients with Stage D2 prostate cancer. In the SWOG study it is usually completed as a self-administered questionnaire, but it has been administered over the telephone for some participants.

UCLA Sexual Functioning Scale

We will assess sexual functioning using a scale developed at University of California – Los Angeles for a study of the quality of life of men treated for localized prostate cancer (28). In developing this scale, investigators held focus groups with 36 prostate cancer patients and their spouses to develop items related to sexual function and the degree of bother caused by problems. After the items were developed their face validity was assessed by additional focus groups of patients and spouses and a panel of health care providers. Items were then pretested in a mailed survey of 40 patients treated in Veterans Affairs hospitals for prostate cancer. The data were factor analyzed and the scale was refined further. The internal consistency and test-retest reliability of this scale are excellent (0.93 and 0.92, respectively). In interviews with the wives, this scale will be modified by eliminating the questions on erectile functioning.

Dyadic Adjustment Scale (DAS)

The DAS, a 32-item scale, measures four components of marital distress: satisfaction, cohesion, consensus, and expression of affection. Internal consistency reliability for the DAS is high (0.96). The scale has been tested extensively with both married and unmarried, cohabiting couples (29). The DAS has been used in several studies focusing on breast cancer patients and couples' experiences with breast cancer (86,87).

(References are provided in protocol reference list)

Protocol ID 97-077

PATHOLOGY REVIEW FORM

UT M.D. Anderson Cancer Center

Patient's Name: _____

Patient No.: _____

No. of slides received: _____ **DOB: :** / / ____ ____ ____

No. of blocks received: _____ **Age:** _____

Designation block/s with tumor: _____ **Race:** _____

Designation block/s without tumor: _____ Date Radical Prostatectomy: ___ / ___ / ___

Block/s representative of tumor: Yes ____ No____ **Date Slides Received:** ____/____/____

Block/s to request: _____ **Date Slides Returned:** ____/____/____

Hormonal ablation: Yes No

Pre-treatment biopsy **Gleason score:** _____ **Gleason grades:** + _____ _____

Radical prostatectomy

Pelvic lymph nodes: **Total** _____ **Positive** _____ **Negative** _____

Gleason score: _____ **Gleason grades:** _____ + _____

Carcinoma Organ confined: **Yes** **No**

Extraprostatic extension: **Yes** **No**

Margin of resection: _____ **Negative** _____ **Positive**

Seminal vesicle involvement: **Yes** **No**

Intraprostatic: _____

Extraprostatic: _____

Histologic type: **Acinar** **Other:**

Notes _____

_____

_____

Reviewing Pathologist:

_____ _____

Patricia Troncoso, M.D. **Date**